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(54) **INFLUENZA VIRUS-LIKE PARTICLES (VLPs) COMPRISING HEMAGGLUTININ PRODUCED WITHIN A PLANT**

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None

See application file for complete search history.

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(57) **ABSTRACT**

A method for synthesizing influenza virus-like particles (VLPs) within a plant or a portion of a plant is provided. The method involves expression of influenza HA in plants and the purification by size exclusion chromatography. The invention is also directed towards a VLP comprising influenza HA protein and plant lipids. The invention is also directed to a nucleic acid encoding influenza HA as well as vectors. The VLPs may be used to formulate influenza vaccines, or may be used to enrich existing vaccines.

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AAGAGTAGTGATATTTTGACAACAATTTTGTTGCAACATTTGAGAAAATTTGTT  
GTTCTCTCTTTTCATTGGTCAAAAACAATAGAGAGAGAAAAAGGAAGAGGGAG  
AATAAAAACATAATGTGAGTATGAGAGAGAAAGTTGTACAAAAGTTGTACCAA  
ATAGTTGTACAAATATCATTGAGGAATTTGACAAAAGCTACACAAATAAGGGTT  
AATTGCTGTAAATAAATAAGGATGACGCATTAGAGAGATGTACCATTAGAGAAT  
TTTTGGCAAGTCATTA AAAAGAAAGAATAAATTTATTTTAAAATTA AAAGTTGAG  
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TCTCTTCTTGTTGGTTCTTCTCAGATCT

**GAGCTC**TAAGTTAAAATGCTTCTTCGTCTCCTATTTATAATATGGTTTGTATTG  
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TTATATTTGAACA ACTAAAATTGAACATCTTTTGCCACA ACTTTATAAGTGGTTA  
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Fig. 1A

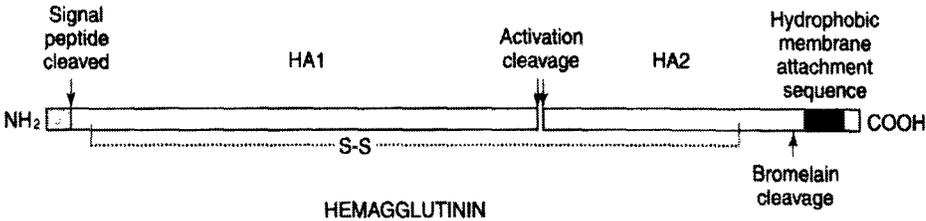


Fig. 1B

Fig. 2A

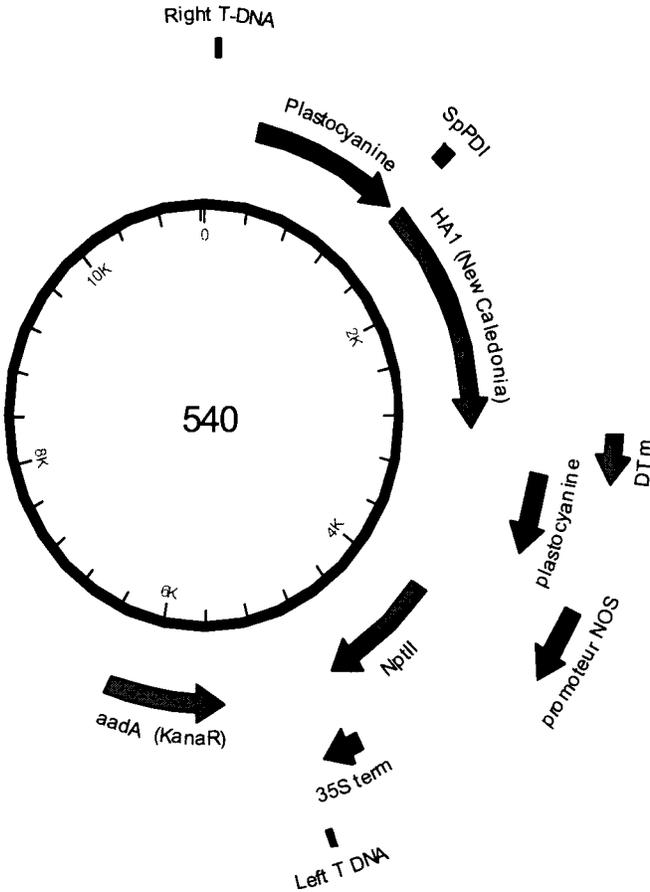


Fig. 2B

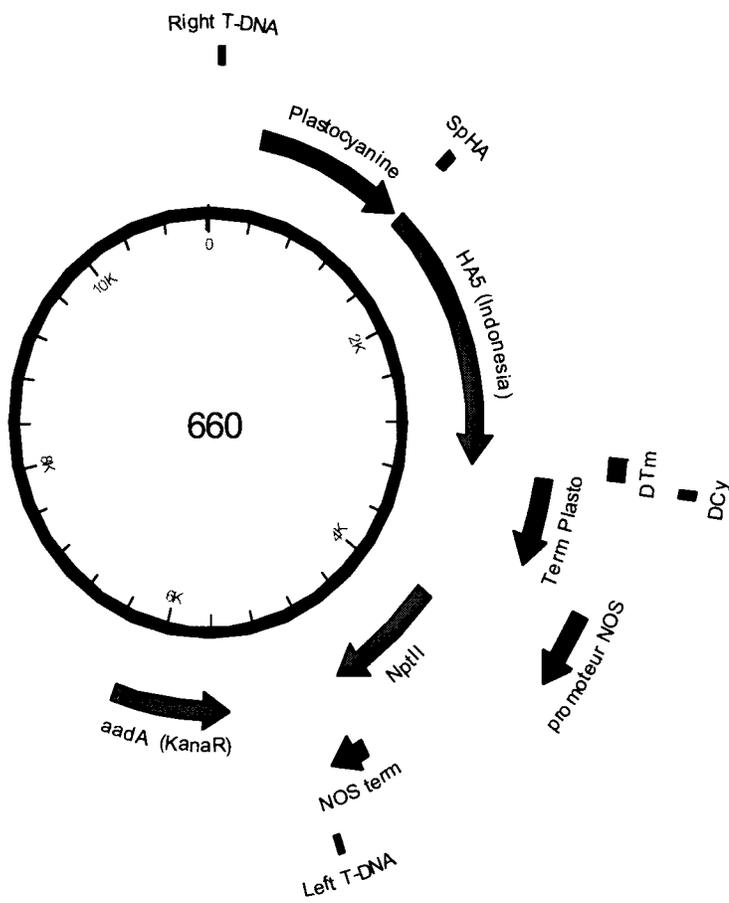


Fig. 3A

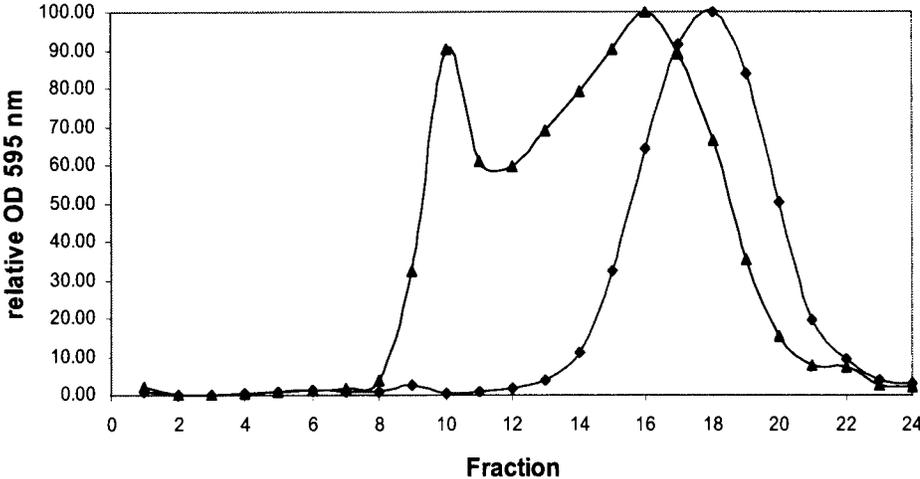


Fig. 3B

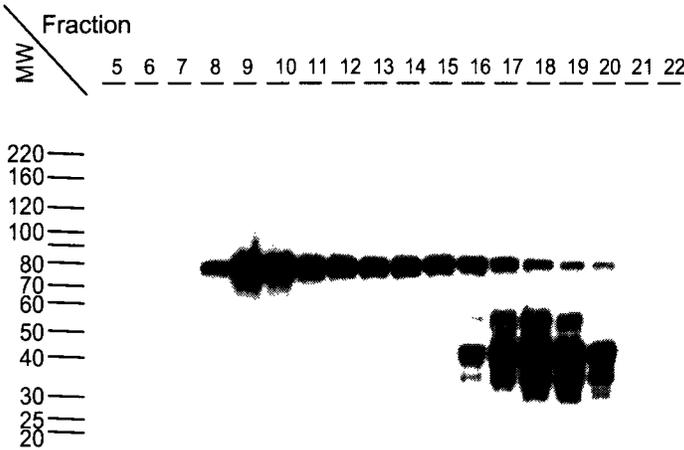


Fig. 3C

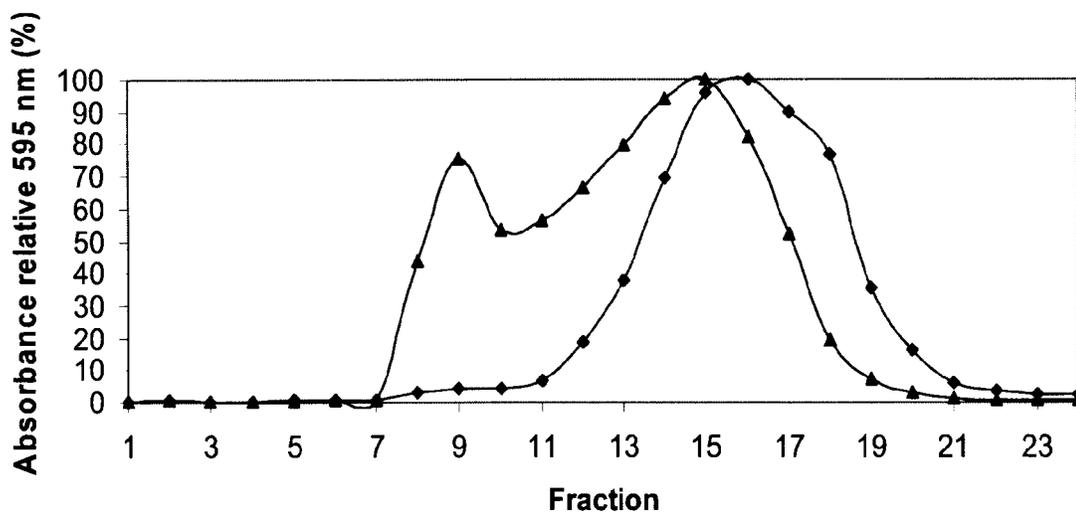


Fig. 3D

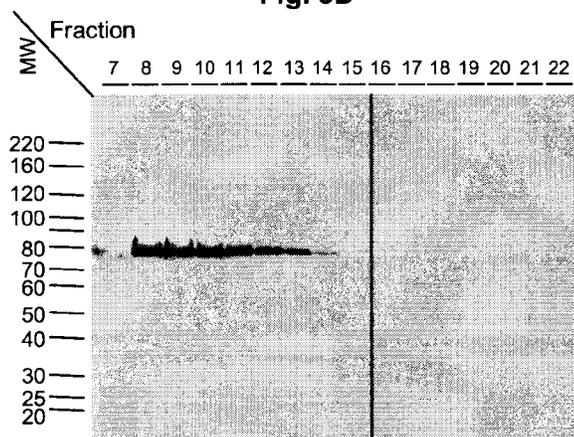


Fig. 4A

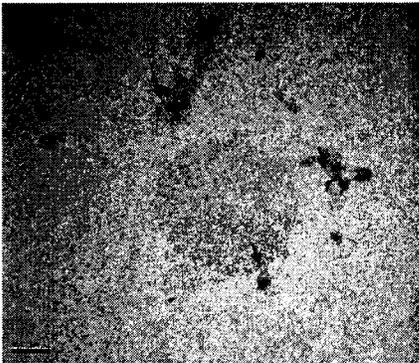


Fig. 4B

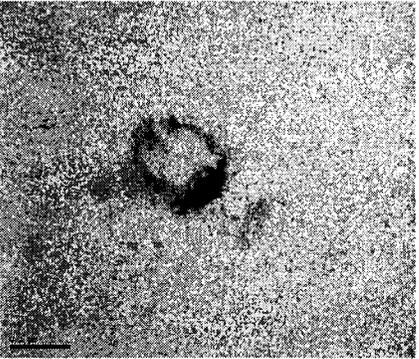


Fig. 4C

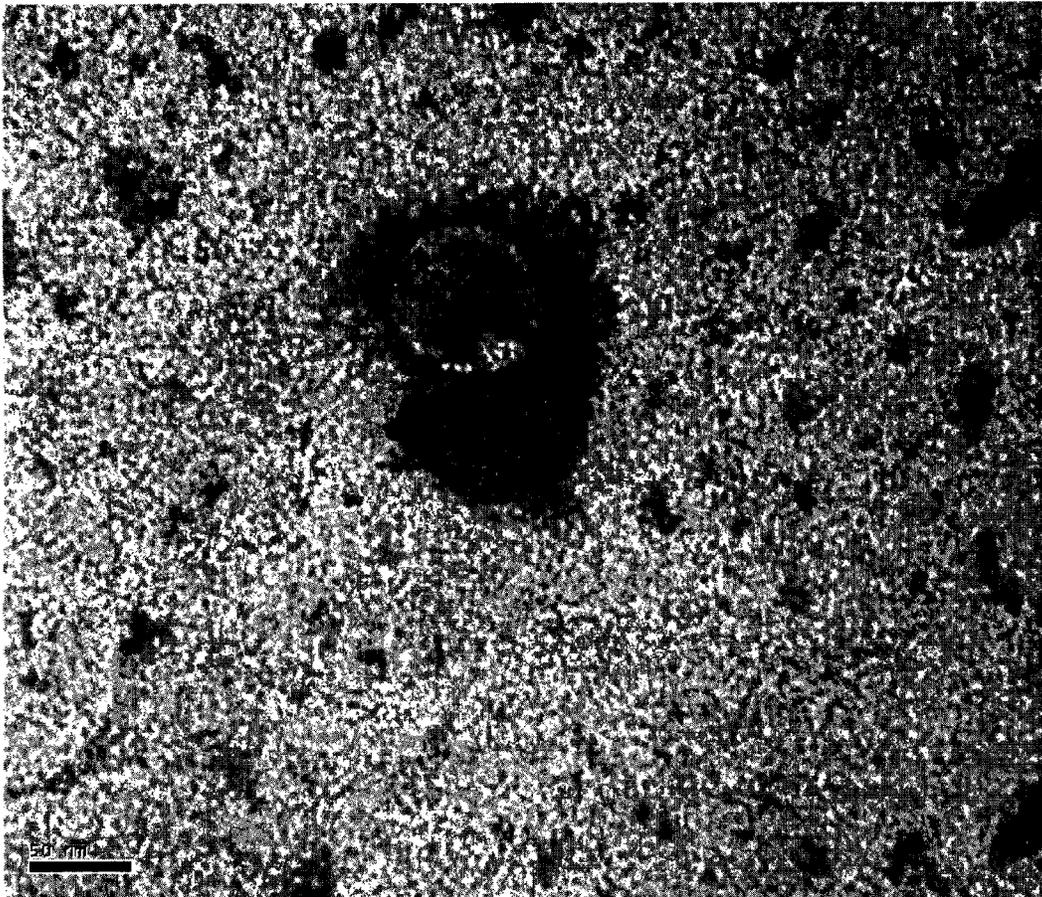


Fig. 5A

SEQ ID NO. 1

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ACTAAAAGGAATAGCCCCACTACAATTGGGTAATTGCAGCGTTGCCGGATGGATCTTAGGAAACCCAGA  
ATGCGAATTACTGATTTCCAAGGAATCATGGTCCTACATTGTAGAAACACCAAATCCTGAGAATGGAACA  
TGTTACCCAGGGTATTTCCGCCACTATGAGGAACTGAGGGAGCAATTGAGTTCAGTATCTTCATTTGAG  
AGATTCGAAATATTCCCCAAAGAAAGCTCATGGCCCAACCACACCGTAACCGGAGTATCAGCATCATGC  
TCCCATAATGGGAAAAGCAGTTTTTACAGAAATTTGCTATGGCTGACGGGGAAGAATGGTTTGTACCCA  
AACCTGAGCAAGTCCATGTAAACAACAAAGAGAAAGATCCTTGTACTATGGGGTGTTCATCACCCG  
CCTAACATAGGGAAACCAAAGGCCACTCTATCATACAGAAAATGCTTATGTCTCTGTAGTGTCTTCACATT  
ATAGCAGAAGATTCACCCCAGAAATAGCCAAAAGACCCAAAGTAAGAGATCAGGAAGGAAGAATCAACT  
ACTACTGGACTCTGCTGGAACCTGGGGATACAATAATATTTGAGGCAAATGGAAATCTAATAGCGCCAT  
GGTATGCTTTTGCAGTGTAGAGGCTTTGGATCAGGAATCATCACCTCAAATGCACCAATGGATGAAT  
GTGATGCCAAGTGTCAAACACCTCAGGGAGCTATAAACAGCAGTCTTCCTTTCCAGAATGTACACCCAG  
TCACAATAGGAGAGTGTCCAAAGTATGTCAGGAGTGCAAAAATTAAGGATGGTTACAGGACTAAGGAACA  
TCCCATCCATTCAATCCAGAGGTTTGTGGAGCCATTGCCGGTTTCATTGAAGGGGGGTGGACTGGAA  
TGGTAGATGGGTGGTATGGTTATCATCATCAGAATGAGCAAGGATCTGGCTATGCTGCAGATCAAAAAA  
GTACACAAAATGCCATTAACGGGATTACAACAAGGTCAATTCTGTAATTGAGAAAATGAACACTCAATT  
CACAGCTGTGGGCAAAGATTCAACAAATTGGAAAGAAGGATGGAAAACCTAAATAAAAAAGTTGATGAT  
GGGTTTCTAGACATTTGGACATATAATGCAGAATTGTTGGTTCTACTGGAAAATGAAAGGACTTTGGATT  
TCCATGACTCCAATGTGAAGAATCTGTATGAGAAAGTAAAAAGCCAATTAAGAATAATGCCAAAGAAAT  
AGGAAACGGGTGTTTTGAGTTCATCACAAAGTGAACAATGAATGCATGGAGAGTGTGAAAAATGGTAC  
CTATGACTATCCAAAATATTCCGAAGAATCAAAGTTAAACAGGGAGAAAATGATGGAGTGAAATTGGAA  
TCAATGGGAGTATACTAAGAGCTCAGGCCT

Fig. 5B

SEQ ID NO. 2

GGTACCTATGACTATCCAAAATATTCCGAAGAATCAAAGTTAAACAGGGAGAAAATTGATGGAGTGAAT  
TGGAAATCAATGGGAGTATACCAGATTCTGGCGATCTACTCAACTGTCGCCAGTCCCTGGTTCTTTGGT  
CTCCCTGGGGGCAATCAGTCTCTGGATGTGTTCCAATGGGTCTTTCAGTGTAGAATATGCATCTAAGA  
GCTCAGGCCT

Fig. 5C

## HA0 from H1 (SEQ ID NO:28)

AGATCTTCGCTGACACAATATGTATAGGCTACCATGCCAACAACTCAACCGACACTGTTGACA  
CAGTACTTGAGAAGAATGTGACAGTGACACACTCTGTCAACCTACTTGAGGACAGTCACAATG  
GAAAATATGTCTACTAAAAGGAATAGCCCCACTACAATTGGGTAATTGCAGCGTTGCCGGAT  
GGATCTTAGGAAACCCAGAATGCGAATTACTGATTTCCAAGGAATCATGGTCTACATTGTAG  
AAACACCAAATCCTGAGAATGGAACATGTTACCCAGGGTATTTCCGCCACTATGAGGAACTGA  
GGGAGCAATTGAGTTCAGTATCTTCATTTGAGAGATTCGAAATATTCCCAAAGAAAGCTCAT  
GGCCCAACCCACACCGTAACCGGAGTATCAGCATCATGCTCCCAATGGGAAAAGCAGTTTTT  
ACAGAAATTTGCTATGGCTGACGGGGAAGAATGGTTTGTACCCAAACCTGAGCAAGTCCTATG  
TAAACAACAAAGAGAAAGAAGTCCTTGTACTATGGGGTGGTTCATCACCCGCCTAACATAGGGA  
ACCAAAGGGCACTCTATCATACAGAAAATGCTTATGTCTCTGTAGTGTCTTCACATTATAGCAG  
AAGATTCACCCAGAAATAGCCAAAAGACCCAAAGTAAGAGATCAGGAAGGAAGAATCAACTA  
CTACTGGACTCTGCTGGAACCTGGGGATACAATAATATTTGAGGCAAATGGAAATCTAATAGC  
GCCATGGTATGCTTTTGCCTGAGTAGAGGCTTTGGATCAGGAATCATCACCTCAAATGCACC  
AATGGATGAATGTGATGCGAAGTGTCAAACACCTCAGGGAGCTATAAACAGCAGTCTTCCTTT  
CCAGAATGTACACCCAGTCACAATAGGAGAGTGTCCAAAGTATGTCAGGAGTGCAAAATTAAG  
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CGGTTTCATTGAAGGGGGGTGGACTGGAATGGTAGATGGGTGGTATGGTTATCATCATCAGA  
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TTGGACATATAATGCAGAATTGTTGGTTCTACTGGAAAATGAAAGGACTTTGGATTCCATGAC  
TCCAATGTGAAGAATCTGTATGAGAAAAGTAAAAAGCCAATTAAGAATAATGCCAAAGAAATAG  
GAAACGGGTGTTTTGAGTCTATCACAAGTGTAAACAATGAATGCATGGAGAGTGTGAAAAATG  
GTACCTATGACTATCCAAAATATTCCGAAGAATCAAAGTAAACAGGGAGAAAATTGATGGAG  
TGAAATTGGAATCAATGGGAGTATACCAGATTCTGGCGATCTACTCAACTGTCGCCAGTTCCC  
TGGTTCTTTTGGTCTCCCTGGGGCAATCAGCTTCTGGATGTGTTCCAATGGGTCTTTGCAGT  
GTAGAATATGCATCTAAGAGCTCAGGCCT

Fig. 6

SEQ ID NO. 3

AAGCTTATGGAGAAAATAGTGCTTCTTCTTGCAATAGTCAGTCTTGTTAAAAGTGATCAGATTTGCATTGG  
TTACCATGCAAAACAATTCAACAGAGCAGGTTGACACAATCATGGAAAAGAAGCTTACTGTTACACATGCC  
CAAGACATACTGGAAAAGACACACAACGGGAAGCTCTGCGATCTAGATGGAGTGAAGCCTCTAATTTTA  
AGAGATTGTAGTGTAGCTGGATGGCTCCTCGGGAACCCAATGTGTGACGAATTCATCAATGTACCGGAA  
TGGTCTTACATAGTGGAGAAGGCCAATCCAACCAATGACCTCTGTTACCCAGGGAGTTTCAACGACTAT  
GAAGAACTGAAACACCTATTGAGCAGAATAAACCATTTTGAGAAAATTCAAATCATCCCCAAAAGTTCTTG  
GTCCGATCATGAAGCCTCATCAGGAGTTAGCTCAGCATGTCCATACCTGGGAAGTCCCTCTTTTTTAGA  
AATGTGGTATGGCTTATCAAAAAGAACAGTACATACCCAACAATAAAGAAAAGCTACAATAATACCAACCA  
AGAGGATCTTTTGGTACTGTGGGGAATTCACCATCCTAATGATGCGGCAGAGCAGACAAGGCTATATCA  
AAACCAACCACCTATATTTCCATTGGGACATCAACACTAAACCAGAGATTGGTACCAAAAAATAGCTACT  
AGATCCAAAGTAAACGGGCAAAGTGGAAGGATGGAGTTCCTTCTGGACAATTTTAAAACCTAATGATGCAA  
TCAACTTCGAGAGTAATGGAAATTTCAATGCTCCAGAATATGCATACAAAATTGTCAAGAAAGGGGACTC  
AGCAATTATGAAAAGTGAATTGGAATATGGTAACTGCAACACCAAGTGTCAAACCTCAATGGGGGCGATA  
AACTCTAGTATGCCATTCCACAACATACACCCTCTACCATCGGGGAATGCCCAAATATGTGAAATCAA  
ACAGATTAGTCCTTGCAACAGGGCTCAGAAATAGCCCTCAAAGAGAGAGCAGAAGAAAAAGAGAGGAC  
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ACCATAGCAATGAGCAGGGGAGTGGGTACGCTGCAGACAAAGAATCCACTCAAAGGCAATAGATGGA  
GTCACCAATAAGGTCAACTCAATCATTGACAAAATGAACACTCAGTTTGAGGCCGTTGGAAGGGAATTTA  
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TAATGCCGAACCTTCTGGTTCTCATGGAAAATGAGAGAATCTAGACTTTTCATGACTCAAATGTTAAGAAC  
CTCTACGACAAGGTCCGACTACAGCTTAGGGATAATGCAAAGGAGCTGGGTAACGGTTGTTTCGAGTTC  
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AAGAAGCAAGATTAAGGAGAGGAAATAAGTGGGTTAAAATTGGAATCAATAGGAACCTACCAAACTACT  
GTCAATTTATTCAACAGTGGCGAGTTCCCTAGCACTGGCAATCATGATGGCTGGTCTATCTTTATGGATG  
TGCTCCAATGGATCGTTACAATGCAGAATTTGCATTTAAGAGCTC

**Fig. 7A**

SEQ ID NO. 4

5'-GTATTAGTAATTAGAATTTGGTGTC-3'

**Fig. 7B**

SEQ ID NO. 5

5'-GCAAGAAGAAGCACTATTTTCTCCATTTTTCTCTCAAGATGATTA-3'**Fig. 7C**

SEQ ID NO. 6

5'-TTAATCATCTTGAGAGAAAATGGAGAAAATAGTGCTTCTTCTTGC-3'**Fig. 7D**

SEQ ID NO. 7

5'-ACTTTGAGCTCTTAAATGCAAATTCTGCATTGTAACGA-3'

**Fig. 8A**

HA1 peptide sequence (SEQ ID NO:9)

**MKAKLLVLLCTFTATYADTICIGYHANNSTDTVDTVLEKNVTVTHSVNLED SHNGKLCLLKGIAPLQ  
LGNCSVAGWILGNPECELLISKESWSYIVETPNPENGTCPYGYFADYEELREQLSSVSSFERFEIFPK  
ESSWPNHTVTGVSASC SHNGKSSFYRNLLWLTGKNGLYPNLSKSYVNNKEKEVLVLWGVHHPPI  
GNQRALYHTENAYVSVSSHYSRRFTPEIAKRPKVRDQEGRINYWTLLLEPGDTIIFEANGNLIAPWY  
AFALSRGFGSGIITSNAPMDECDACKQTPQGAINSSLPFQNVHPVTIGECPKYVRS AKLRMVTGLRNI  
PSIQSRGLFGAIAGFIEGGWTGMVDGWYGYHHQNEQGSYAADQKSTQNAINGITNKVNSVIEKMN  
TQFTAVGKEFNKLERRMENLNKKVDDGFLDIWTYNAELLVLENERTLDFHDSNVKNLYEKVKSQK  
NNAKEIGNGCFEFYHKCNNECMESVKNGTYDYPKYSEESKLNREKIDGVKLESMGVYQILAIYSTVA  
SSLVLLVSLGAISFWMCSNGSLQCRICI\***

**Fig. 8B**

HA5 peptide sequence (SEQ ID No: 10)

**MEKIVLLLAIVSLVKS DQICIGYHANNSTEQVDTIMEKNVTVTHAQDILEKTHNGKLC DLDGVKPLILR  
DCSVAGWLLGNPMCDEFINVPEWSYIVEKANPTNDLCYPGSFN DYEELKHLLSRINHFEKIQIIPKSS  
WSDHEASSGVSSACPYLGSPSFFRN VVWLIKKNSTYPTIKKSYNNTNQEDLLVLWGIHHPNDAAEQ  
TRLYQNPTTYISIGTSTLNQRLVPKIATR SKVNGQSGRMEFFWTILKPNDAINFESNGNFIAPEYAYKI  
VKKGDSAIMKSELEYGNCNTKCQTPMGAINSSMPFHNIHPLTIGECPKYV KSNRLVLATGLRNSPQR  
ESRRKKRGLFGAIAGFIEGGWQGMVDGWYGYHHSNEQGSYAADKESTQKAIDGVTNKVNSIIDK  
MNTQFEAVGREFNLERRIENLNKKMEDGFLDVWTYNAELLVLMENERTLDFHDSNVKNLYDKVRL  
QLRDNAKELGNGCFEFYHKCDNECMESIRNGTYNYPQYSEEARLKREEISGVKLESIGTYQILSIYST  
VASSLALAIMMAGLSLWMCSNGSLQCRICI\***

Fig. 9

**Subtype H7 (SEQ ID NO:11)**

>BHB940420|gb:AF071776|Symbol:HA|Name:hemagglutinin precursor|Organism:Influenza A Virus A/chicken/New York/1995|Chromosome:4|Subtype:H7|Host:Avian

GACAAAATATGTCTTGGGCACCATGCTGTGGCAAATGGAACAAAAGTGAACACATTAACAGAGAGGGGGA  
TTGAAGTAGTGAACGCCACAGAGACGGTGGAAACTGCGAATATCAAGAAAATATGTATTCAGGGAAAAG  
GCCAACAGATCTGGGACAATGTGGACTTCTAGGAAACCCTAATAGGACCTCCCCAATGTGATCAATTCCTG  
GAGTTTTACTCTGATTTGATAATTGAGCGAAGAGAAGGAACCGATGTGTGCTATCCCGGTAATTCACAA  
ATGAAGAATCACTGAGGCAGATCCTTCGAGGGTCAGGAGGAATTGATAAGGAGTCAATGGGTTTCACCTA  
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ACAAACCAGCTCTGATAATTTGGGGAGTTCATCACTCTGGATCGGTTAGCGAGCAGACCAAACTCTATGG  
AAGTGGAAACAAGTTGATAACAGTAGGAAGCTCAAAATACCAGCAATCATTCACCCCAAGTCCGGGAGCA  
CGCCACAAGTGAATGGACAATCAGGGAGAATCGATTTTCACTGGCTACTCCTTGATCCCAATGACACAG  
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AGTCCAGAGTGTATGTTCTCTGGATTCTAGTTGTGGAGGGGATTGCTTTCACAGTGGGGGTACGATAGTC  
AGTTCCTGCCATTCCAAAACATCAACCCTAGAAGTGTGGGGAGATGCCCTCGGTATGTCAAACAGACAA  
GCCTCCTTTTGGCTACAGGAATGAGAAATGTTCCAGAGAATCCAAAGCCCAGAGGCCCTTTTGGAGCAAT  
TGCTGGATTCATAGAGAATGGATGGGAGGGTCTCATCGATGGATGGTATGGTTTCAGACATCAAAATGCA  
CAAGGGGAAGGAACTGCAGCTGACTACAAAAGCACCCAATCTGCAATAGATCAGATCACAGGCAAATGA  
ATCGTCTGATTGACAAAACAAATCAGCAGTTTGAGCTGATAGACAATGAGTTCAATGAGATAGAACAACA  
AATAGGAAATGTCATTAATTGGACACGAGACGCAATGACTGAGGTATGGTCGTATAATGCTGAGCTGTTG  
GTGGCAATGGAAAATCAGCATACAATAGATCTTGC GGACTCAGAAATGAACAACTTTATGAGCGTGTCA  
GAAAACAACCTTAGGGGAGAAATGCTGAAGAAGATGGAACCTGGATGTTTTGAGATATTCATAAGTGTGATGA  
TCAGTGCATGGAGAGCATAAGGAACAACACTTATGACCATACTCAATACAGAACAGAGTCATTGCAGAAT  
AGAATACAGATAGACCAGTGAAATTGAGTAGTGGATACAAAAGACATAATCTTATGGTTTAGCTTCGGGG  
CATCATGTTTTCTTCTTAGCCGTTGTAATGGGATTGGTTTTCATTTGCATAAAGAAATGGAAACATGCC  
GTGCACCATTTGATATAA

Fig. 10A

**Subtype H2 (SEQ ID NO:12)**

>gi|408516|gb|L11132.1|FLADE88HA Influenza A virus (A/herring gull/DE/677/88 (H2N8))  
hemagglutinin (HA) gene, complete cds

```
AGCAAAAGCAGGGGTTATACCATAGACAACCAAAGGCAAGACAATGGCCATCATTATCTAATCTTCTG
TTCACAGCAGTGAGAGGGGACCAAATATGCATTGGATACCATCCAACAATCCACAGAAAAGGTTGACA
CAATCCTAGAGAGAAATGTCACTGTGACTCACGCTGAGGACATTCTTGAGAAGACTCACAATGGGAAGTT
ATGCAAATAAATGGAATCCCTCCACTTGAATTAAGGGATTGCAGCATTGCCGGATGGCTCCTTGGGAAT
CCAGAATGTGATATACTTCTAACTGTGCCAGAATGGTCATACATAATAGAAAAAGAAAATCCAAGGAACG
GCTTGTGCTACCCAGGCAGTTTCAATGATTATGAAGAATGAAGCATCTTATCAGCAGCGTGACACATTT
TGAGAAAGTAAAGATTCTGCCCAGAAATGAATGGACACAGCATACAACAACCTGGAGGTTACAGGCTGC
GCAGACTATGGTGGTCCCGTCATTCTCCGGAACATGGTCTGGTTGACAAAAGAAAGGGTCGAATTATCCAA
TTGCCAAAAGATCTTACAACAATACAAGTGGGGAACAAATGCTGATCATTGGGGGATACATCACCCCAA
TGATGAAAGTGAACAAAGAGCATTGTATCAGAATGTGGGGACCTATGTGTCAGTAGGAACATCAACACTG
AACAAAAGATCATCCCCAGAAATAGCAACAAGACCTAAAGTGAATGGACAAGGAGGCAGAATGGAATTCT
CGTGGACTATCTTAGATATATGGGACACAATAAATTTTGAGAGTACTGGCAATCTAATTGCACCAGAATA
TGGTTTCAAATATCCAACGAGGTAGTTTCAGGGATCATGAAAACAGAAGGAAAACCTGAAAACCTGCGAG
ACCAAGTGCCAAACTCCTTTGGGAGCAATAAATACAACATTACCCTTTCACAATATCCACCCACTGACCA
TTGGTGAGTGCCCAAATATGTAAAAATCGGAAAGATTAGTCTTAGCAACAGGACTAAGAAACGTCCCTCA
GATTGAGTCAAGGGGATTGTTTGGGGCAATAGCTGGTTTTATAGAGGGTGGATGGCAAGGAATGGTTGAT
GGTTGGTATGGGTATCATCACAGCAATGACCAGGGATCTGGGTATGCAGCAGACAAAGAATCCACTCAA
AGGCAATTGATGGAATCACCAACAAGGTAATTTCTGTGATCGAAAAGATGAACACCCAATTCGGAGCTGT
TGAAAAAGAATTCAGTAACCTGGAGAGAAGACTGGAGAACCTGAAATAAAAAGATGGAGGACGGATTTCTA
GATGTGTGGACATACAATGCCGAGCTCCTAGTTCTAATGGAAAATGAGAGGACACTTGACTTTCATGATT
CTAATGTCAAGAATCTATATGATAAAGTCAGAATGCAACTGAGAGACAATGCAAAAGAACTAGGGAAATGG
ATGTTTTGAATTTTATCACAAATGTGATGATGAATGCATGAACAGTGTGAAGAATGGGACATATGATTAT
TCCAAGTATGAAGAGGAGTCTAAACTAAACAGGACTGAAATCAAAGGGGTTAAATGAGCAATATGGGGG
TTTATCAAATCCTTGCCATCTATGCTACAGTAGCAGGTTCCTTGTCTGACTGGCAATCATGATAGCTGGGAT
TTCTATATGGATGTGCTCCAACGGGTCTCTGCAATGCAGAATCTGCATATGATCATCAGTCATTTTGTAA
TTAAAAACACCCCTTGTCTACT
```

**Fig. 10B****Subtype H3 (SEQ ID NO:13)**

>BHB2107299|gb:EF473574|Symbol:HA|Name:hemagglutinin|Organism:Influenza A  
Virus A/Texas/32/2003|Segment:4|Subtype:H3|Host:Human

CAAAAACCTCCCGGAAATGACAACAGCACGGCAACGCTGTGCCTTGGGCACCATGCAGTACCAAACGGAA  
CGATAGTGAAAACAATCACGAATGACCAAATTGAAGTTACTAATGCTACTGAGCTGGTACAGAGTTCCTC  
AACAGGTGGAATATGCGACAGTCCTCATCAGATCCTTGATGGAGAAAACCTGCACACTAATAGATGCTCTA  
TTGGGAGACCCTCAGTGTGATGGCTTCCAAAATAAGAAATGGGACCTTTTTGTTGAACGCAGCAAAGCCT  
ACAGCAACTGTTACCCTTATGATGTGCCGGATTATGCCTCCCTTAGGTCACTAGTTGCCTCATCCGGCAC  
ACTGGAGTTTAAACAATGAAAGCTTCGATTGGACTGGAGTCACTCAGAATGGAACAAGCTCTGCTTGCAAA  
AGGAGATCTAATAAAAGTTTCTTTAGTAGATTGAATTGGTTGACCCACTTAAAATACAAATACCCAGCAT  
TGAACGTGACTATGCCAAACAATGAAAAATTTGACAAATTGTACATTTGGGGGGTTCACCACCCGGGTAC  
GGACAGTGACCAAATCAGCCTATATGCTCAAGCATCAGGAAGAATCACAGTCTCTACCAAAGAAGCCAA  
CAAACGTGTAATCCCGAATATCGGATCTAGACCCAGGGTAAGGGATGTCTCCAGCCGAATAAGCATCTATT  
GGACAATAGTAAACCCGGGAGACATACTTTTGATTAACAGCACAGGGAATCTAATTGCTCCTCGGGGTTA  
CTTCAAAATACGAAGTGGGAAAAGCTCAATAATGAGATCAGATGCACCCATTGGCAAATGCAATTCGGAA  
TGCATCACTCCAAATGGAAGCATTCCCAATGACAAACCATTTCAAATGTAAACAGGATCACATATGGGG  
CCTGTCCCAGATATGTTAAGCAAAACACTCTGAAATTGGCAACAGGGATGCGAAATGTACCAGAGAAACA  
AACTAGAGGCATATTTGGCGCAATCGCGGGTTTCATAGAAAATGGTTGGGAGGGAATGGTGGACGGTTGG  
TACGGTTTCAGGCATCAAATTTCTGAGGGCACAGGA

Fig. 10C

**Subtype H4 (SEQ ID NO:14)**

>BHB1050162|gb:DQ021859|Symbol:HA|Name:hemagglutinin|Organism:Influenza A Virus  
A/mallard/MN/33/00|Segment:4|Subtype:H4|Host:Avian

ATGCTATCAATCACGATTCTGTTTCTGCTCATAGCAGAGGGTTCCTCTCAGAATTACACAGGGAATCCCG  
TGATATGCCTGGGACATCATGCCGTATCCAATGGGACAATGGTGAACCCCTGACTGATGACCAAGTAGA  
AGTTGTCCTGCCCCAAGAATTAGTGAATCGCAACATCTACCGGAGTTGTGTCCTAGCCCTTTAAGATTA  
GTAGATGGACAAACTTGTGACATCGTCAATGGTGCCTTGGGGAGTCCAGGCTGTGATCACTTGAATGGTG  
CAGAATGGGATGTC TTCATAGAACGCCACTGCTGTGGACACTGTTATCCATTTGATGTGCCGGATTA  
CCAGAGCCTACGGAGTATCCTAGCAAACAATGGGAAATTTGAGTTCATTGCTGAGGAATTCCAATGGAAC  
ACAGTCAAACAAAATGGGAAATCCGGAGCATGCAAAGAGCAAATGTGAATGACTTTTTCAACAGATTGA  
ACTGGCTGACCAAATCTGATGGGAATGCATACCCACTTCAAACCTGACAAAGGTTAACAACGGGGACTA  
TGCAAGACTTTACATATGGGGAGTTCATCATCCTTCAACTGACACAGAACAACCAACTTGTATAAGAAC  
AACCCCTGGGAGAGTAACTGTTTCCACAAAACCAGTCAAACAAGTGTGGTACCAAACATTTGGCAGTAGAC  
CATGGGTAAGAGGCCAAAGCGGCAGGATTAGCTTCTATTGGACAATTTGGGAGCCAGGAGACCTCATAGT  
CTTCAACACCATAGGGAATTTAATGCTCCGAGAGGTCATTACAAGCTTAACAGTCAAAGAAGAGCACA  
ATTCTGAATACTGCAATTCCTATAGGATCTTGTGTTAGTAAATGTCACACAGATAGGGGTTCAATCTCTA  
CAACCAACCCTTTCAGAACATCTCAAGAATATCAATGGGGACTGTCCCAAGTATGTCAAACAGGGATC  
CTTGAAACTAGCTACAGGAATGAGGAATATCCCTGAGAAAGCAACCAGAGGCCTGTTTGGTGCAATTG

**Fig. 10D****Subtype H5 (SEQ ID NO:15)**

>BHB950029|gb:AF501235|Symbol:HA|Name:hemagglutinin|Organism:Influenza A Virus  
A/duck/Shanghai/1/2000|Segment:4|Subtype:H5|Host:Avian

ATGGAGAAAATAGTGCTTCTTCTTGAATAGTCAGTCTTGTTAAAAGTGATCAGATTTGCATTGGTTACC  
ATGCAAAACAACTCGACAGAGCAGGTTGACACAATAATGGAAAAGAACGTTACTGTTACACATGCCCAAGA  
CATACTGGAAAAGACACACAACGGGAACTCTGCGATCTAGATGGAGTGAAGCCTCTAATTTTGAGAGAT  
TGTAGTGTAGCTGGATGGCTCCTCGGAAACCTATGTGTGACGAATTCATCAATGTGCCGGAATGGTCTT  
ACATAGTGGAGAAGGCCAGTCCAGCCAATGACCTCTGTTACCCAGGGGATTTCAACGACTATGAAGAACT  
GAAACACCTATTGAGCAGAATAAACCACTTTGAGAAAATTCAGATCATCCCCAAAAGTTCTTGGTCCAAT  
CATGAAGCCTCATCAGGGGTGAGCGCAGCATGTCCATACCATGGGAAGCCCTCCTTTTTCAGAAATGTGG  
TATGGCTTATCAAAAAGAACAGTGCATACCCAACAATAAAGAGGAGCTACAATAATACCAACCAAGAAGA  
TCTTTTGGTACTGTGGGGGATTCCACATCCTAATGATGCGGCAGAGCAGACAAAGCTCTATCAAAACCA  
ACCACCTATATTTCCGTTGGAACATCAACACTAAACCAGAGATTGGTCCCAAAAATAGCTACTAGATCCA  
AAGTAAACGGGCAAAGTGAAGAATGGAGTCTTCTGGACAATTTTAAAGCCGAATGATGCCATAAATTT  
CGAGAGTAATGGAATTTTCATTGCTCCAGAATATGCATACAAAATTTGTCAAGAAAGGGGACTCAGCAATT  
ATGAAAAGTGAATGGAATATGGTAACTGCAACACCAAGTGTCAAACCTCAATGGGGGCGATAAACTCTA  
GTATGCCATTCCACAACATACACCTCTCACAATCGGGGAATGCCCAATATGTGAAATCAAACAGATT  
AGTCTTGGCGACTGGACTCAGAAATACCCCTCAAAGAGATAGAAGAAGAAAAAGAGAGGACTATTTGGA  
GCTATAGCAGGTTTTATAGAGGGGAGGATGGCAAGGAATGGTAGATGGTTGGTATGGGTACCACCATAGCA  
ATGAGCAGGGGAGTGGATACGCTGCAGACAAAGAATCCACTCAAAGGCAATAGATGGAGTCACCAATAA  
GGTCAACTCGATCATTGACAAAATGAACACTCAGTTTGAGGCCGTTGGAAGGGAATTTAATAACTTAGAA  
AGGAGGATAGAAAATTTAAACAAGAAGATGGAAGACGGATTCCCTAGATGTCTGGACTTATAATGCTGAAC  
TTCTGGTTCTCATGGAAAATGAGAGAACTCTAGACTTTCATGATTCAAATGTCAAGAACCTTTACAACAA  
GGTCCGACTACAGCTTAGGGATAATGCAAAGGAGCTGGGTAATGGTTGTTTCGAGTTCTATCACAATGT  
GATAATGAATGTATGGAAAGTGTAAAAACGGGACGTATGACTACCCGCGATTTCAAGAAGCAAGAC  
TAAACAGAGAGGAAAATAAGTGGAGTAAAATGGAATCAATGGGAACTTACCAAATACTGTCAATTTATTC  
AACAGTGGCGAGTTCCCTAGCACTGGCAATCATGGTAGCTGGTCTATCTTTATGGATGTGCTCCAATGGG  
TCGTTACAATGCAGAATTTGCATTTAA

Fig. 10E

**Subtype H6 (SEQ ID NO:16)**

>BHB1049778|gb:DQ021667|Symbol:HA|Name:hemagglutinin|Organism:Influenza A Virus  
A/northern pintail/TX/828189/02|Segment:4|Subtype:H6|Host:Avian

ATGATTGCAATCATTGTAATAGCGATACTGGCAGCAGCCGGAAAGTCAGACAAGATCTGCATTGGGTATC  
ATGCCAACAATTCAACAACACAGGTGGATACGATACTTGAGAAGAATGTAACCGTCACACACTCAGTTGA  
ATTGCTGGAGAATCAGAAGGAAGAAAGATTCTGCAAGATCTTGAACAAGGCCCTCTCGACCTAAAGGGA  
TGCACCATAGAGGGTTGGATCTTGGGGAATCCCAATGCGATCTGTTGCTTGGTGACCAAAGCTGGTCAT  
ATATAGTGGAAAGACCTACTGCCAAAATGGGATATGCTACCCAGGAGCTTTGAATGAGGTAGAAGAACT  
GAAAGCATTTATCGGATCAGGAGAAAGGGTAGAGAGATTTGAGATGTTCCCAAAGCACATGGGCAGGG  
GTAGACACCAGCAGTGGGGTAACAAAAGCTTGTCCCTTATAATAGTGGTTCATCTTTCTACAGAAACCTCC  
TATGGATAATAAAGACCAAGTCAGCAGCGTATCCAGTAATTAAGGGAACCTACAGCAACACTGGAAACCA  
GCCAATCCTCTATTTCTGGGGTGTGCACCATCCCTGACACCAATGAGCAAAATACTCTGTATGGCTCT  
GGCGATCGGTATGTTAGGATGGGAACTGAGAGCATGAATTTTGCCAAGAGCCCAGAAATTGCGGCAAGAC  
CCGCTGTGAATGGCCAAAGAGGTCGAATTGATTATTACTGGTCTGTTTTAAAACCAGGAGAAACCTTGAA  
TGTGGAATCTAATGGAAATCTAATCGCTCCTTGGTATGCATACAAATTTGTCAACACAAAATAAAGGGA  
GCCGCTTCAAGTCAAATTTACCAATCGAGAATTGCGATGCCACATGCCAGACTATTGCAGGAGTCCTAA  
GGACCAATAAAACATTTCAGAATGTGAGCCCTCTGTGGATAGGAGAATGCCCAAGTATGTGAAAAGTGA  
AAGTCTAAGGCTTGCTACTGGACTAAGAAATGTTCCACAGATTGAAACCAGAGGGCTTTTCGGAGCTATC

**Fig. 10F****Subtype H8 (SEQ ID NO:17)**

>gi|221317|dbj|D90304.1|FLAH8N4 Influenza A virus  
(A/Turkey/Ontario/6118/68(H8N4)) gene for hemagglutinin precursor, complete  
cds

ATGGAAAATTCATCGCAATAGCAACCTTGGCGAGCACAAATGCATACGATAGGATATGCATTGGGTACC  
AATCAAACAACCCACAGACACAGTGAACACTCTCATAGAACAGAATGTACCAGTCACCCAAACAATGGA  
GCTCGTGGAAACAGAGAAACATCCCGCTTATTGTAACACTGATTTAGGTGCCCCATTGGAAGTGCAGAGAC  
TGCAAGATTGAGGCAGTAATCTATGGGAACCCCAAGTGTGACATCCATCTGAAGGATCAAGGTTGGTCAT  
ACATAGTGGAGAGGCCAGCGCACCAGAAGGGATGTGTTACCCTGGATCTGTGGAAAATCTAGAAGAACT  
GAGGTTTGTCTTCCAGTGCTGCATCTTACAAGAGAATAAGACTATTTGACTATTCCAGGTGGAATGTG  
ACTAGATCTGGAACGAGTAAAGCATGCAATGCATCAACAGGTGGCCAATCCTTCTATAGGAGCATCAATT  
GGTTGACCAAAAAGGAACCAGACACTTATGACTTCAATGAAGGAGCTTATGTTAATAATGAAGATGGAGA  
CATCATTTTCTTATGGGGATCCATCATCCGCCGGACACAAAAGAGCAGACAACACTATATAAAAAATGCA  
AACACTTTGAGTAGTGTACTACTAACACTATAAACAGAAGCTTCAACCAAATATTGGTCCCAGACCAT  
TAGTAAGAGGACAGCAAGGGAGGATGGATTACTATTGGGGCATTCTGAAAAGAGGGGAGACTCTGAAGAT  
CAGGACCAACGGAAATTTAATCGCACCTGAATTTGGCTATCTGCTCAAAGGTGAAAGCTACGGCAGAATA  
ATTCAAAATGAGGATATACCCATCGGGAACGTAAACACAAAATGTCAAACATATGCGGGAGCAATCAATA  
GCAGCAAACCCTTTCAAGATGCAAGTAGGCATTACATGGGAGAATGTCCCAAATATGTGAAGAAGGCAAG  
CTTGGCACTTGCAGTTGGGCTTAGGAATACGCCTTCTGTTGAACCCAGAGGACTGTTTGGAGCCATTGCT  
GGTTTCATTGAAGGAGGATGGTCTGGAATGATTGATGGGTGGTATGGATTTTCATCACAGCAATTCAGAGG  
GAACAGGAATGGCAGCTGACCAGAAATCAACACAAGAAGCCATCGATAAGATCACCAATAAAGTCAACAA  
TATAGTTGACAAGATGAACAGGGAGTTTGAAGTTGTGAATCATGAGTTCCTGAAGTTGAAAAAGAATA  
AACATGATAAACGATAAAATAGATGACCAAATGAAGATCTTTGGGCTTACAATGCAGAGCTCCTTGTGC  
TCTTAGAGAACCAGAAAACGCTAGACGAACATGATCCAATGTCAAAAACCTTTTGTGATGAAGTGAAGAAG  
GAGACTGTCAGCCAATGCAATAGATGCTGGGAACGGTTGCTTTGACATACTTACAAAATGCGACAATGAG  
TGTATGGAAACTATAAAGAACGGAACCTTACGATCATAAGGAATATGAAGAGGAGGCTAAACTAGAAAAGGA  
GCAAGATAAATGGAGTAAACTAGAAGAGAACACCACCTTACAAAATCTTTAGCATTACAGTACAGTGGC  
GGCCAGTCTTTGCTTGGCAATCCTGATTGCTGGAGGTTAATCCTGGGCATGCAAAAATGGATCTTGTAGA  
TGCATGTTCTGTATTGA

Fig. 10G

**Subtype H9 (SEQ ID NO:18)**

>BHB954830|gb:AM087218|Symbol:HA|Name:hemagglutinin|Organism:Influenza A Virus  
A/shoveler/Iran/G54/03|Segment:4|Subtype:H9|Host:Avian

ATGGAAACAGTATCACTAATGACTATACTACTAGTAGCAACAGCAAGCAATGCAGACAAAATCTGCATCG  
GCCACCAGTCAACAAACTCCACAGAACTGTGGACACGCTAACAGAAACCAATGTTCCCTGTGACACATGC  
CAAAGAATTGCTCCACACAGAGCACAATGGAATGCTGTGTGCAACAAATCTGGGACATCCCCTAATCTTA  
GACACGTGCACTATTGAAGGACTGATCTATGGTAACCCCTTCTTGTGACTTGCTGTTGGGAGGAAGAGAAT  
GGTCTACATCGTCGAAAGGTCAACAGCTGTAAATGGAACGTGTACCTGGGAATGTAGAGAACC TAGA  
GGAATCAGGACACTTTTTAGTTCGGCTAGTTCCTACCGAAGAATCCAAATCTTCCAGACACAATCTGG  
AATGTGACTTACACTGGAACAAGCAAAGCATGTTCCAGATTCATTCTACAGGAGTATGAGATGGCTGACTC  
AAAAAAGCGGGTCTTACCCTGTTCAAGACGCTCAATACAAAATAATATGGGAAAGAGCATTCTTTTCGT  
GTGGGGCATAATCACCACCCACTGAAGCTGCACAGACAAATTTGTACACAAGAACCGACACAACAACA  
AGCGTGACAACAGAAGACTTAAATAGGATCTTCAAACCGATGGTAGGGCCAAGGCCCTTGTC AATGGTC  
TGCAGGGAAGAATTAATTATTATGGTCGGTACTAAAACCAGGCCAGACACTGCGAGTAAGATCCAATGG  
GAATCTAATTGCTCCATGGTATGGACACATTCTTTCGGGAGGGAGCCATGGAAGAATCCTGAAGACTGAT  
TTAAAAAGTAGTAATTGCGTAGTGCAATGTGCAACTGAAAAGGGCGCTTAAACAGTACATTGCCGTCC  
ACAATATCAGTAAATATGCATTTGGAAACTGTCCCAAATATGTTAGAGTAAAAGTCTCAAACCTGGCAGT  
AGGGTTGAGGAACGTGCCTGCTAGATCAAGTAGAGGACTATTCGGAGCCATAGCTGGATT CATAGAAGGA  
GGTTGGCCAGGACTAGTCGCTGGTTGGTATGGTTTCCAGCATTCAAATGATCAAGGGGTGGTATTGCGG  
CAGATAGGGATTCAACTCAAAGGCAATTGATAGAATAACAACCAAGGTGAATAATATAGTCGACAAAAT  
GAACAACAATATGAAATAATTGATCATGAATTCAGTGAGGTTGAAACTAGGCTCAACATGATCAATAAT  
AAGATTGATGACCAAATACAAGACATATGGGCATATAATGCAGAGTTGCTAGTACTACTTGAAAACCAGA  
AAACACTCGATGAGCATGACGCAAATGTGAAGA

Fig. 10H

**Subtype H10 (SEQ ID NO:19)**

>gi|324365|gb|M21647.1|FLAMS84HA Influenza A virus  
(A/chicken/Germany/N/1949(H10N7)) hemagglutinin precursor, gene,  
complete cds

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AGCAAAAGCAGGGGTCACAATGTACAAAGTAGTAGTAATAATTGCGCTCCTTGAGCAGTGAAAGGTCTT
GACAGAATCTGCCTAGGACACCATGCGGTTGCCAATGGAACCATTGTGAAGACCCTTACAAATGAACAAG
AGGAAGTGACCAATGCTACTGAGACGGTAGAGAGCACAAATTTGAATAAATTGTGTATGAAAGGAAGAAG
CTACAAGGACTTGGGCAATTGTCCACCGGTAGGAATGTTGATAGGAACACCTGTTTGTGATCCGCACCTG
ACCGGGACCTGGGACACTCTCATTGAGCGAGAGAATGCCATTGCCACTGTTATCCAGGGGCAACCATAA
ATGAAGAAGCATTGAGGCAGAAAATAATGGAAAGTGGAGGAATCAGCAAGATGAGCACTGGCTTCACTTA
TGGGTCTTCCATCACCTCAGCTGGGACCACTAAGGCATGCATGAGAAATGGAGGAGATAGTTTCTATGCA
GAGCTCAAATGGCTAGTGTCAAAGACAAAGGGACAAAATTTCCCTCAGACAACAAACACCTATCGGAATA
CGGACACAGCAGAACATCTCATAATATGGGGAATTCATCACCCCTCCAGCACACAGGAAAAGAATGACTT
ATACGGAACCTCAGTCACTATCTATATCAGTTGAGAGTTCACATATCAGAACAACCTTTGTCCAGTTGTT
GGGGCAAGACCTCAGGTC AATGGACAAAGTGGGCGAATTGACTTTC ACTGGACACTAGTACAGCCGGGTG
ACAACATAACCTTCTCAGACAATGGAGGTCTAATAGCACCAAGTCGAGTTAGCAAATTA ACTGGAAGGGA
TTTGGGAATCCAATCAGAAGCGTTGATAGACAACAGTTGTGAATCCAAATGCTTTTGGAGAGGGGGTTCT
ATAAATACAAAGCTCCCTTTTCAAATCTGTCAACCAGAACAGTAGGTC AATGCCCAAATACGTAAATC
AGAGGAGTTTACTGCTTGCAACAGGGATGAGGAATGTGCCAGAAGTGGTGCAGGGAAGGGGCTGTGTTGG
TGCAATAGCAGGGTTCATAGAAAACGGATGGGAAGGAATGGTAGACGGCTGGTATGGTTTCAGACACCAA
AATGCCAGGGCACAGGCCAAGCTGCTGATTACAAGAGTACTCAAGCAGCTATTGACCAAATCACAGGGA
AACTGAACAGGTGATTGAGAAGACCAACACTGAGTTTGAGTCAATAGAATCTGAATTCAGTGAGACTGA
GCATCAAATGGTAACGTCAATTAATGGACCAAAGATTCAATAACCGACATTTGGACTTACAACGCAGAG
CTATTAGTGGCAATGGAGAATCAGCACACAATTGACATGGCTGATTCAGAGATGCTAAATCTGTATGAAA
GGGTAAGAAAGCAACTCAGACAGAATGCAGAAGAAGACGGAAAGGGATGTTTTGAGATATATCATACTTG
TGATGATTCGTGCATGGAGAGTATAAGGAACAATACTTATGACCATTCACAATACAGAGAGGAGGCTCTT
CTGAATAGACTGAACATCAACCCAGTGAAACTTCTTCGGGGTACAAAGACATCATACTTTGGTTTAGCT
TCGGGGAATCATGCTTTGTTCTTCTAGCCGTTGTTATGGGTCTTGTGTTTCTTCTGCCTGAAAAATGGAAA
CATGCGATGCACAATCTGTATTTAGTTAAAAACACCTTGTCTTCTACT
```

**Fig. 10I****Subtype H11 (SEQ ID NO:20)**

>gi|221307|dbj|D90306.1|FLAHAH11N Influenza A virus (A/duck/England/56(H11N6)) gene for hemagglutinin precursor, complete cds

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ATGGAGAAAACACTGCTATTTGCAGCTATTTTCCTTTGTGTGAAAGCAGATGAGATCTGTATCGGGTATT
TAAGCAACAACCTCGACAGACAAAGTTGACACAATAATTGAGAACAATGTCACGGTCACTAGCTCAGTGGA
ACTGGTTGAGACAGAACACACTGGATCATTCTGTTCAATCAATGGAAAACAACCAATAAGCCTTGGAGAT
TGTTCAATTTGCTGGATGGATATTAGGAAACCCTATGTGTGATGAACTAATTGGAAAGACTTCATGGTCTT
ACATTGTGGAAAAACCAATCCAACAAATGGAATCTGTTACCCAGGAACTTTAGAGAGTGAAGAAGAACT
AAGACTGAAATTCAGTGGAGTTTTAGAATTTAACAAATTCGAAGTATTCACATCAAATGGATGGGGTGTCT
GTAATTCAGGAGTAGGAGTAACCGCTGCATGCAAATTCGGGGTTCTAATTCCTTCTTTTCGAAACATGG
TATGGCTGATACACCAATCAGGAACATATCCTGTAATAAAGAGAACCTTTAACACACCAAAGGGAGAGA
TGTAAGTATGTTTTGGGGAATTCATCATCCTGCTACACTGACAGAACATCAAGATCTGTATAAAAAGGAC
AGCTCCTATGTAGCAGTGGGTTTCAGAGACCTACAACAGAAGATTCACTCCAGAAATCAACACTAGGCCCA
GAGTCAATGGACAGGCCGGACGGATGACATTTACTGGAAGATAGTCAAACCAGGAGAATCAATAACATT
CGAATCTAATGGGGCGTTCCCTAGCTCCTAGATATGCTTTTGAGATTGTCTCTGTTGGAAATGGGAACTG
TTCAGGAGCGAACTGAACATTGAATCATGCTCTACCAAATGTCAAACAGAAATAGGAGGAATTAATACGA
ACAAAAGCTTCCACAATGTTACAGAAACACTATCGGGGATTGCCCAAGTATGTGAATGTCAAATCCTT
AAAGCTTGCAACAGGACCTAGAAATGTCCAGCAATAGCATCGAGAGGCTTGTGGAGCAATAGCTGGA
TTCATAGAAGGGGGATGGCCTGGACTGATCAATGGATGGTATGGGTCCAACACAGGGACGAAGAAGGAA
CAGGCATTCGACAGCAGACAAGGAGTCAACTCAAAAGGCAATAGACCAGATAACATCCAAGGTAATAACAT
CGTTGACAGGATGAATACAACTTTGAGTCTGTGCAACACGAATTCAGTGAATAGAGGAAAGAAATAAAT
CAATTATCAAAACACGTAGATGATTCTGTGGTTGACATCTGGTCATATAATGCACAGCTTCTCGTTTTAC
TTGAAAATGAGAAGACACTGGACCTCCATGACTCAAATGTGAGGAACTCCATGAGAAAAGTCAGAAAGAT
GCTAAAGGACAATGCCAAAGATGAGGGGAACGGATGCTTACCTTTTACCATAAGTGTGACAATAAATGC
ATTGAACGAGTTAGAAACCGAACATATGATCATAAAGAATTCGAGGAGGAATCAAAAATCAATCGCCAGG
AGATTGAAGGGGTGAAACTAGATTCTAGTGGGAATGTGTATAAAAATACTGTCAATTTACAGCTGCATTGC
AAGCAGTCTTGTATTGGCAGCACTCATCATGGGGTTCATGTTTTGGGCATGCAGTAATGGATCATGTAGA
TGTAACATTTGCATTTAG
```

Fig. 10J

**Subtype H12 (SEQ ID NO:21)**

>gi|221309|dbj|D90307.1|FLAHAH12N Influenza A virus (A/duck/Alberta/60/76(H12N5)) gene for hemagglutinin precursor, complete cds

```
ATGGA AAAAATTCATCATTTTGGAGTACTGTCTTGGCAGCAAGCTTTGCATATGACAAAATTTGCATTGGAT
ACCAAACAACAACCTCGACTGAAACGGTAAACACACTAAGTGAACAAAACGTTCCGGTGACGCAGGTGGA
AGA ACTTG TACATCGTGGGATTGATCCGATCCTGTGTGGAACGGA ACTAGGATCACCACTAGTGCTTGAT
GACTGTT CATTAGAGGGTCTAATCCTAGGCAATCCCAAATGTGATCTTTATTTGAATGGCAGGGAATGGT
CATA CATAGTAGAGAGGCCCAAAGAGATGGAAGGAGTTTGC TATCCAGGGTCAATTGAAAACCAGGAAGA
GCTAAGATCTCTGTTTTCTTCCATCAAAAAATATGAAAGAGTGAAGATGTTTGATTTACCAAATGGAAT
GTCACATACACTGGGACCAGCAAGGCCTGCAATAATACATCAAACCAAGGCTCATTCTATAGGAGCATGA
GATGGTTGACCTTAAATCAGGACAATTTCCAGTCCAAACAGATGAGTACAAGAACACCAGAGATT CAGA
CATTGTATTCACCTGGGCCATTCACCACCCACCAACATCTGATGAACAAGTAAAATTATACAAAAATCCT
GATACTCTCTCTTCAGTCAACCACCGTAGAAATCAATAGGAGCTTCAAGCCTAATATAGGGCCAAGACCAC
TCGTGAGAGGACAACAAGGGAGAATGGATTACTACTGGGCTGTTCTTAAACCTGGACAAACAGTCAAAT
ACAAACCAATGGTAATCTTATTGCACCTGAATATGGTCACTTAATCACAGGGAAATCACATGCCAGGATA
CTCAAGAATAATTTGCCCATGGGACAGTGTGTGACTGAATGTCAATTGAACGAGGGTGTAAATGAACACAA
GCAAACCTTTCCAGAACACTAGTAAGCACTATATTTGGGAAATGCCCAAATACATACCATCAGGGAGTTT
AAAATTGGCAATAGGGCTCAGGAATGTCCACAAGTTC AAGATCGGGGGCTCTTTGGAGCAATTGCAGGT
TTCATAGAAGGCGGATGGCCAGGGCTAGTGGCTGGTTGGTACGGATTT CAGCATCAAAATGCGGAGGGGA
CAGGCATAGCTGCAGACAGAGACAGCACCCAAAGGGCAATAGACAATATGCAAAACAAC TCAACAATGT
CATCGACAAAATGAATAAACAATTTGAAGTGGTGAATCATGAGTTTTCAGAAGTGGAAAGCAGAATAAAC
ATGATTAATTCAAAATTGATGATCAGATAACTGACATATGGGCATACAATGCTGAATTGCTTGTCTAT
TGGAAAATCAGAAGACATTAGATGAGCATGACGCTAATGTAAGGAATCTACATGATCGGGTCAGAAGAGT
CCTGAGGGAAAATGCAATGACACAGGAGACGGCTGCTTTGAGATTTTACATAAATGTGACACAATTTGT
ATGGACACGATTAGAAACGGGACATACAATCACAAAGAGTATGAGGAAGAAAGCAAATCGAACGACAGA
AAGTCAATGGTGTGAAACTTGAGGAGAATTTACATATAAAATTTCTGAGCATCTACAGCAGTGTGCCTC
AAGCTTAGTTCTACTGCTCATGATTATTTGGGGTTTTCATTTTCGGGTGTCAAAATGGAAATGTTTCGTTGT
ACTTTCTGTATTTAA
```

Fig. 10K

**Subtype H13 (SEQ ID NO:22)**

>gi|221311|dbj|D90308.1|FLAHAH13N Influenza A virus  
(A/Gull/Maryland/704/77 (H13N6)) gene for hemagglutinin precursor, complete cds

ATGGCTCTAAATGTCATTGCAACTTTGACACTTATAAGTGTATGTGTACATGCAGACAGAATATGCGTGG  
GGTATCTGAGCACCAATTCATCAGAAAGGGTCGACACGCTCCTTGAAAATGGGGTCCCAGTCACCAGCTC  
CATTGATCTGATTGAGACAAACCACACAGGAACATACTGTTCTCTAAATGGAGTCAGTCCAGTGCATTTG  
GGAGATTGCAGCTTTGAAGGATGGATTGTAGGAAACCCAGCCTGCACCAGCAACTTTGGGATCAGAGAGT  
GGTCATACTGATTGAGGACCCCGCGGCCCTCATGGGCTTTGCTACCCTGGAGAATTAAACAACAATGG  
TGAACCTCAGACACTTGTTCAGTGGAAATCAGGTCATTTCAGTAGAACGGAATTGATCCCACCTACCTCCTGG  
GGGGAAGTACTTGACGGTACAACATCTGCTTGCAGAGATAACACGGGAACCAACAGCTTCTATCGAAATT  
TAGTTTGGTTTATAAAGAAGAATACTAGATATCCAGTTATCAGTAAGACCTACAACAATACAACGGGAAG  
GGATGTTTTAGTTTTATGGGGAATACATCACCCAGTGTCTGTGGATGAGACAAAGACTCTGTATGTCAAT  
AGTGATCCATACACTGGTTTTCCACCAAGTCTTGGAGCGAGAAATATAAACTAGAAACGGGAGTCCGAC  
CTGGCTATAATGGACAGAGGAGCTGGATGAAAATTTATTGGTCTTTGATACATCCAGGGGAGATGATTAC  
TTTCGAGAGTAATGGTGGATTTTTAGCCCAAGATATGGGTACATAATTGAAGAATATGGAAAAGGAAGG  
ATTTTCCAGAGTCGCATCAGAATGTCTAGGTGCAACACCAAGTGCCAGACTTCGGTTGGAGGGATAAACA  
CAAACAGAACGTTCCAAAACATCGATAAGAATGCTCTTGGTGACTGTCCAAAATACATAAAGTCTGGCCA  
ACTCAAGCTAGCCACTGGACTCAGAAATGTGCCAGCTATATCGAATAGAGGATTGTTCCGAGCAATTGCA  
GGGTTCATAGAAGGAGGCTGGCCAGGTTAATCAATGGTTGGTACGGTTTTTCAGCATCAAAATGAACAGG  
GAACAGGAATAGCTGCAGACAAAGAATCAACACAGAAAGCTATAGACCAGATAACAACCAAAATAAATAA  
CATTATTGATAAAATGAATGGGAACATGATTCAATTAGGGGTGAATTCAATCAAGTTGAGAAGCGTATA  
AACATGCTTGCAGACAGAATAGATGATGCCGTGACGGACATTTGGTCATACAATGCCAAACTTCTTGTAT  
TGCTGGAAAATGATAAAACTTTAGATATGCATGATGCTAATGTAAAGAATTTACATGAGCAAGTACGAAG  
AGAATTGAAGGACAATGCAATTGACGAAGGAAATGGCTGTTTTGAACTCCTTCATAAATGCAATGACTCC  
TGCATGGAACTATAAGAAATGGAACGTATGACCACACTGAGTATGCAGAGGAGTCAAAGTTAAAGAGGC  
AAGAAATCGATGGGATCAAACCTCAAATCAGAAGACAACGTTTACAAAGCATTATCAATATACAGTTGCAT  
TGCAAGTAGTGTGTACTAGTAGGACTCATACTCTCTTTCATCATGTGGGCCTGTAGTAGTGGGAATTGC  
CGATTCAATGTTTGTATATAA

Fig. 10L

**Subtype H14 (SEQ ID NO:23)**

>gi|324045|gb|M35997.1|FLAH1424 Influenza A/Mallard/Gurjev/263/82  
hemagglutinin subtype H14 gene

AGCAAAAGCAGGGGAAAATGATTGCACTCATATTGGTTGCACTGGCTCTGAGCCCACTGCTTATTCTCA  
GATCACAATGGGACAACAGGAAACCCATTATATGCTTGGGGCATCATGCAGTGGAAAACGGCACATCT  
GTTAAAACACTAACAGACAATCACGTAGAAGTTGTGTGTCAGCTAAAGAATTAGTTGAGACGAACCACACTG  
ATGAACTGTGCCAAGCCCTTGAAGCTTGTGCGACGGGCAAGACTGCCACCTCATCAATGGTGCATTGGG  
GAGTCCAGGCTGTGACCGTTTGCAGGACACCACTTGGGATGTCTTCATTGAAAGGCCCACTGCAGTAGAC  
ACATGTTATCCATTTCGACGTCCAGATTACCAGAGTCTCAGAAGCATCCTAGCAAGCAGTGGGAGTTTGG  
AGTTCATCGCCGAACAATTCACCTGGAATGGTGTCAAAGTTGACGGATCAAGCAGTGCTTGTGTTGAGGGG  
CGGTCGCAACAGCTTCTTCTCCCGACTAAACTGGCTAACCAAAGCAACAATGGAACTATGGACCTATT  
AACGTCATAAAGAAAATACGGGCTCTTATGTGCTAGGCTCTATCTCTGGGGAGTGCATCACCCATCAAGCG  
ATAATGAGCAAACGGATCTCTACAAGGTGGCAACAGGGAGAGTAACAGTATCTACCCGCTCGGACCAAAAT  
CAGTATTGTTCCCAATATAGGAAGTAGACCGAGGGTAAGGAATCAGAGCGGCAGGATAAGCATCTACTGG  
ACCCTAGTAAACCCAGGGGACTCCATCATTTTCAACAGTATTGGGAATTTGATTGCACCAAGAGGCCACT  
ACAAAATAAGCAAATCTACTAAGAGCACAGTGCTTAAAAGTGACAAAAGGATTGGGTCATGCACAAGCCC  
TTGCTTAACTGATAAAGGTTTCGATCCAAAGTGACAAACCTTTTCAGAATGTATCAAGGATTGCTATAGGA  
AACTGCCCGAAATATGTAAAGCAAGGGTCCCTGATGTTAGCAACTGGAATGCGCAACATCCCTGGCAAAC  
AGGCAAAGGGCTTATTTGGGGCAATTGCTGGATTTCATTGAAAATGGTTGGCAAGGCCTGATTGATGGGTG  
GTATGGATTTCAGGCACCAAAAATGCTGAAGGAACAGGAACTGCTGCAGACCTGAAGTCAACTCAGGCAGCC  
ATTGATCAGATAAATGGCAAGCTGAACAGATTGATAGAGAAGACAAATGAAAAATATCACCAATAGAAA  
AGGAATTCGAACAGGTGGAAGGAAGAATACAAGACCTTGAGAAGTACGTTGAGGACACTAAGATTGATTT  
GTGGTCATAAATGCTGAATTGCTAGTAGCACTAGAGAATCAGCACACAATAGATGTCACAGACTCCGAA  
ATGAACAAGCTTTTTGAAAGAGTAAGAAGGCAATTAAGAGAGAATGCAGAAGATCAAGGCAACGGTTGTT  
TCGAGATATTCCATCAGTGTGACAACAATTGTATAGAAAGCATTAGAAACGGAACCTTATGACCACAACAT  
CTACAGGGATGAAGCCATCAACAATCGAATCAAAAATAAATCCTGTCACTTTGACGATGGGGTACAAGGAC  
ATAATCCTGTGGATTTCTTCTCCATGTCATGCTTTGTCTTCGTGGCACTGATTCTGGGATTTGTTCTAT  
GGGCTTGTCAAACGGGAATATCCGATGCCAAATCTGTATATAAAGAAAAAACACCCCTGTTTCTACTC

Fig. 10M

**Subtype H15 (SEQ ID NO:24)**

>gi|1226068|gb|L43916.1|FLAHEMAC Influenza A/duck/Australia/341/83 (H15N8) hemagglutinin mRNA, complete cds

```
AGCAAAAGCAGGGGATACAAAATGAACACTCAAATCATCGTCATTCTAGTCCTCGGACTGTCGATGGTGA
GATCTGACAAGATTTGTCTCGGGCACCATGCCGTAGCAAATGGGACAAAAGTCAACACACTAACTGAGAA
AGGAGTGGAAGTGGTCAATGCCACGGAGACAGTGGAGATTACAGGAATAAATAAAGTGTGCACAAAAGGG
AAGAAAGCGGTGGACTTGGGATCTTGTGGAATACTGGGAACTATCATTGGGCCTCCACAATGTGACTCTC
ATCTTAAATTCAAAGCTGATCTGATAATAGAAAGAAGAAATTCAGTGACATCTGTTACCCAGGGAAATT
CACTAATGAGGAAGCACTGAGACAAATAATCAGAGAATCTGGTGGAAATTGACAAAGAGCCAATGGGATTT
AGATATT CAGGAATAAAAACAGACGGGGCAACCAGTGCCTGTAAGAGAACAGTGTCTCTTTCTACTCAG
AAATGAAATGGCTTTTATCCAGCAAGGCTAACCCAGGTGTTCCACAACTGAATCAGACATACAGGAACAA
CAGAAAAGAACCCAGCCCTAATTGTTTGGGGAGTACATCATCAAGTTCCTTGGATGAGCAAAAATAAGCTA
TATGGAGCTGGGAACAAGCTGATAACAGTAGGAAGCTCAAATACCAACAATCGTTTTCCCAAGTCCAG
GGGACAGGCCCAAAGTGAATGGTCAGGCCGGGAGGATCGACTTTCATTGGATGCTATTGGACCCAGGGGA
TACAGTCACTTTTACCTTCAATGGTGCATT CATAGCCCCAGATAGAGCCACCTTTCTCCGCTCTAATGCC
CCATCGGGAGTTGAGTACAATGGGAAGTCACTGGGAATACAGAGTGATGCACAAATTGATGAATCATGTG
AAGGGAAATGCTTCTACAGTGGAGGGACAATAAACAGCCCTTTGCCATTTCAAACATCGATAGTTGGGC
TGTCGGAAGGTGCCCCAGATATGTAAAGCAATCAAGCCTGCCGCTGGCCTTAGGAATGAAAAATGTACCA
GAGAAAAATACATACTAGGGGACTGTTCCGTGCAATTGCAGGATTCATCGAGAATGGATGGGAAGGACTCA
TTGATGGATGGTATGGATTTAGGCATCAAAAATGCACAGGGGCAGGAAACAGCTGCTGACTACAAGAGTAC
TCAGGCTGCAATTGACCAGATAACAGGGAACTTAATAGATTAATTGAAAAAACCAACACACAGTTTGAA
CTCATAGACAATGAGTTCACTGAAGTGGAGCAGCAGATAGGCAATGTAATAAACTGGACAAGGGACTCCT
TGACTGAGATCTGGTCATACAATGCTGAACTTCTAGTAGCAATGGAAAATCAGCATACAATTGACCTTGC
AGATTCTGAAATGAACAACTCTATGAGAGAGTGAGAAGACAGCTAAGGGAGAATGCCGAGGAGGATGGA
ACTGGATGTTTTGAGATTTCCACCGATGTGACGATCAATGTATGGAGAGCATACGAAATAATACTTACA
ATCACACTGAATATCGACAGGAAGCCTTACAGAATAGGATAATGATCAATCCGGTAAAGCTTAGTGGTGG
GTACAAAAGATGTGATACTATGGTTAGCTTCGGGGCATCATGTGTAATGCTTCTAGCCATTGCTATGGGT
CTTATTTTCATGTGTGTGAAAAACGGGAATCTGCCGTGCACTATCTGTATATAAATATTTGAAAAACACC
CTTGTTTCTACT
```

Fig. 10N

**Subtype H16 (SEQ ID NO:25)**

>gi|56425020|gb|AY684891.1| Influenza A virus (A/black-headed gull/Sweden/5/99(H16N3)) hemagglutinin (HA) gene, complete cds

```
AGCAAAGCAGGGGATATTGTCAAACAACAGAATGGTGATCAAAGTGCTCTACTTTCTCATCGTATTGT
TAAGTAGGTATTCGAAAGCAGACAAAATATGCATAGGATATCTAAGCAACAACGCCACAGACACAGTAGA
CACACTGACAGAGAACGGAGTTCAGTGACCAGCTCAGTTGATCTCGTTGAAACAACCCACACAGGAACA
TACTGCTCACTGAATGGAATCAGCCCAATTCATCTTGGTGACTGCAGCTTTGAGGGATGGATCGTAGGAA
ACCCTTCCCTGTGCCACCAACATCAACATCAGAGAGTGGTCGTATCTAATTGAGGACCCCAATGCCCCAA
CAAACCTCTGCTTCCCAGGAGAGTTAGATAATAATGGAGAATTACGACATCTCTTCAGCGGAGTGAACCTCT
TTTAGCAGAACAGAATTAATAAGTCCCAACAAATGGGGAGACATTTGGATGGAGTCACCGCTTCTTGCC
GCGATAATGGGGCAAGCAGTTTTTACAGAAATTTGGTCTGGATAGTGAAGAATAAAAATGGAAAATACCC
TGTCATAAAGGGGATTACAATAACACAACAGGCAGAGATGTTCTAGTACTCTGGGGCATTCCACCATCCG
GATACAGAAAACAACAGCCATAAACTTGACGCAAGCAAAAACCCCTACACATTAGTATCAACAAAGGAAT
GGAGCAAAGATATGAACAGTAAATGGCACCAGAAATAGGTGATGGACAGAGAAGTTGGATGAAACTATA
TTGGCACCTCATGCGCCCTGGAGAGAGGATAATGTTTTGAAAGCAACGGGGGCCCTTATAGCGCCAGATAC
GGATACATCATTGAGAAGTACGGTACAGGACGAATTTCCAAAGTGGAGTGAGAATGGCCAAATGCAACA
CAAAGTGTCAAACATCATTAGGTGGGATAAAACCCAACAAAACCTTTCCAAAACATAGAGAGAAATGCTCT
TGGAGATTGCCCAAAGTACATAAAGTCTGGACAGCTGAAGCTTGCAACTGGGCTGAGAAATGTCCCATCC
GTTGGTGAAGAGGTTTTTGGTGCAATTGCAGGCTTCATAGAAGGAGGGTGGCTGGGCTAATTAATG
GATGGTATGTTTTCCAGCATCAGAATGAACAGGGGACTGGCATTGCTGCAGACAAAGCCTCCACTCAGAA
AGCGATAGATGAAATAACAACAAAATTAACAATATAATAGAGAAGATGAACGGAAACTATGATCAATA
AGAGGGGAATCAATCAAGTAGAAAAGAGGATCAACATGCTCGCTGATCGAGTTGATGATGCAGTAACTG
ACATATGGTTCGTACAATGCTAAACTTCTTGTACTGCTTGAAAATGGGAGAACATTGGACTTACACGACGC
AAATGTCAGGAACCTTACACGATCAGGTCAAGAGAATATTGAAAAGTAATGCTATTGATGAAGGAGATGGT
TGCTTCAATCTTCTTACAAAATGTAATGACTCATGCATGGAAACTATTAGAAAATGGGACCTACAATCATG
AAGATTACAGGGAAGAATCACAACCTGAAAAGGCAGGAAATTGAGGGAATAAAATTGAAGTCTGAAGACAA
TGTGTATAAAGTACTGTGATTTATAGCTGCATTGCAAGCAGTATTGTGCTGGTAGGTCTCATACTTGCG
TTCATAATGTGGGCATGCAGCAATGGAAATGCCGGTTAATGTTGTATATAGTCGGAAAAAATACCCCT
TGTTTTCTACT
```

Fig. 100

**Influenza B (SEQ ID NO:26)**

>gi|325175|gb|K00423.1|FLBHAZO Influenza B/Lee/40, hemagglutinin (seg 4), complete segment

AGCAGAAGCGTTGCATTTTCTAATATCCACAAAATGAAGGCAATAATTGTACTACTCATGGTAGTAACAT  
CCAATGCAGATCGAATCTGCACTGGGATAACATCGTCAAACCTCACCTCATGTGGTTAAAACCTGCCACTCA  
AGGGGAAGTCAATGTGACTGGTGTGATACCACCTAACAAACACCTACCAAATCTCATTTTGCAAATCTC  
AAAGGAACACAGACCAGAGGAAAACCTATGCCCAAACCTGTTTTAACTGCACAGATCTGGACGTGGCCCTAG  
GCAGACCAAATGCATGGGGAACACACCCTCCGCAAAAAGTCTCAATACTCCATGAAGTCAAACCTGCTAC  
ATCTGGATGCTTTCCTATAATGCACGACAGAACAAAAATCAGACAACCTACCTAATCTTCTCAGAGGATAT  
GAAAACATCAGGTTATCAACCAGTAATGTTATCAATACAGAGACGGCACCAGGAGGACCCTACAAGGTGG  
GGACCTCAGGATCTTGCCCTAACGTTGCTAATGGGAACGGCTTCTTCAACACAATGGCTTGGGTTATCCC  
AAAAGACAACAAGACAGCAATAAATCCAGTAACAGTAGAAGTACCATAACATTTGTTTCAAGAGGGGAA  
GACCAAATTAAGTGTGGGGTCCACTCTGATGACAAAACCAAATGGAAAGACTCTATGGAGACTCAA  
ATCCTCAAAGTTACCTCATCTGCCAATGGAGTAACCACACATTATGTTTCTCAGATTGGTGGCTTCCC  
AAATCAAACAGAAGACGAAGGGCTAAAACAAAGCGGCAGAATTGTTGTTGATTACATGGTACAAAAACCT  
GGAAAAACAGGAACAATTGTTTATCAAAGAGGCATTTTATGCCTCAAAAAGTGTGGTGCAGTGGCA  
GGAGCAAGGTAATAAAAAGGGTCTTGCCTTTAATTGGTGAAGCAGATTGCCTCCACGAAAAGTACGGTGG  
ATTAATAAAAAGCAAGCCTTACTACACAGGAGAGCATGCAAAGGCCATAGGAAATGCCCAATATGGGTG  
AAAACACCCTTGAAGCTGGCCAATGGAACCAAATATAGACCGCTGCAAAACTATTAAGGAAAGAGGTT  
TCTTCGGAGCTATTGCTGGTTTCTTGAAGGAGGATGGGAAGGAATGATTGCAGGTTGGCACGGATACAC  
ATCTCATGGAGCACATGGAGTGGCAGTGGCAGCAGACCTTAAGAGTACACAAGAAGCTATAACAAGATA  
ACAAAAAATCTCAACTATTTAAGTGAAGTGAAGTAAAAACCTTCAAAGACTAAGCGGAGCAATGAATG  
AGCTTCACGACGAAATACTCGAGCTAGACGAAAAGTGGATGATCTAAGAGCTGATACAATAAGCTCACA  
AATAGAGCTTGCAGTCTTGCTTTCCAACGAAGGGATAATAAACAGTGAAGATGAGCATCTCTTGGCCTT  
GAAAGAAAACCTGAAGAAAATGCTTGGCCCCTCTGCTGTAGAAAATAGGGAATGGGTGCTTTGAAACCAAC  
ACAAATGCAACCAGACTTGCCTAGACAGGATAGCTGCTGGCACCTTTAATGCAGGAGATTTTCTCTTCC  
CACTTTTGATTCAATTAACATTACTGCTGCATCTTTAAATGATGATGGCTTGGATAATCATACTATACTG  
CTCTACTACTCAACTGCTGCTTCTAGCTTGGCTGTAACATTAATGATAGCTATCTTATTGCTTACATGG  
TCTCCAGAGACAATGTTTCTTGTCCATCTGTCTGTGAGGGAGATTAAGCCCTGTGTTTTCTTTACTGT  
AGTGCTCATTGCTTGTCCACATTACAAAGAAACGTTATTGAAAATGCTCTGTACTACT

Fig. 10P

**Influenza C (SEQ ID NO:27)**

```
>gi|325317|gb|M17868.1|FLCHAJ0 Influenza C/Johannesburg/66
hemagglutinin esterase RNA (seg 4), complete cds
AGCAGAAGCAGGGGGTTAATAATGTTTTCTCATTACTCTTGGTGTGGGCCTCACAGAGGCTGAAAAAA
TAAAGATATGCCTTCAAAAAGCAAGTGAACAGTAGCTTCAGCCTACACAATGGCTTCGGAGGAAATTTGTA
TGCCACAGAAGAAAAAGAATGTTTGAGCTTGTAAAGCCCAAAGCTGGAGCCTCTGTCTTGAATCAAAGT
ACATGGATTGGCTTTGGAGATTCAAGGACTGACAAAAGCAATTCAGCTTTTCCTAGGTCTGTGATGTTT
CAGCAAAAACCTGCTGATAAGTTTCGTTTTTGTCTGGTGGATCCTTAATGTTGAGTATGTTTGGCCCACC
TGGGAAGGTAGACTACCTTTACCAAGGATGTGGAAAACATAAAGTTTTTATGAAGGAGTTAACTGGAGT
CCACATGCTGCTATAAATGTTACAGAAAAAATTGGACTGATATCAAACCTGAATTTCCAGAAAAACATTT
ATGAATTTGGCTTCAACATCACATTGCATGAGCTTGGTGAATGCCTTGGACAAAACCTATTCCTTTACAAGT
GACTGCTGGGATGCAGGAATTTGCAACAACAGCTTCTTAAAAAATCCAGCATTGTACACACAAGAAGTC
AAGCCTTCAGAAAAACAAATGTGGGAAAGAAAACTTGTCTTCTTCACTTCCAACCCAATTTGGAACTT
ATGAGTGCAAACCTGCATCTTGTGGCTTCTTGCATTTTCACTATGATAGTAAAGAAGTGTACAATAAAAG
AGGATGTGACAACTACTTTCAAGTGTCTATGATTCATTTGGAAAAGTCGTTGGAGGACTAGATAACAGG
GTATCACCTTACACAGGGAATCTGGAGACACCCCAACAATGCAATGTGACATGCTCCAGCTGAAACCTG
GAAGATATTCAGTAAGAAGCTCTCCAAGATTCCTTTTAAATGCCTGAAAAGAAGTTATTGCTTTGACATGAA
AGAAAAAGGACCAGTCACCTGCTGTCCAATCCATTTGGGGAAAAGGCAGAGAATCTGACTATGCAGTGGAT
CAAGCTTGCTTGAGCACCTCAGGGTGCATGTTGATCCAAAAGCAAAGCCATACATTGGAGAAGCTGATG
ATCACCATGGAGATCAAGAAATGAGGGAGTTGCTGTGAGGACTGGACTATGAAGCTAGATGCATATCACA
ATCAGGGTGGGTGAATGAAACCAGTCTTTTACGGAGAAAATACCTCCTTCTCCCAAATTTGGAAGATGC
CCTTTGGCTGCAAAGGAAGAATCCATTCAAAAATCCCAGATGGCCTTCTAATCCCACCAGTGGAAACCG
ATACCACTGTAACCAACCTAAGAGCAGAATTTTGGAAATCGATGACCTCATTATTTGGTGTGCTCTTTGT
TGCAATCGTTGAAAACAGGAATTTGGAGGCTATCTGCTTGGAAAGTAGAAAAGAATCAGGAGGAGGTGTGACA
AAAGAATCAGCTGAAAAGGGTTTGAGAAAATTGGAAATGACATACAAAATTTTAAAATCTTCTATAAATA
TCGCAATAGAAAAACTAAAATGACAGAATTTCTCATGATGAGCAAGCCATCAGAGATCTAACTTTAGAAAT
TGAAAATGCAAGATCTGAAGCTTTATTTGGGAGAATTGGGAATAATAAGAGCCTTATTGGTAGGAAATATA
AGCATAGGATTACAGGAATCTTTATGGGAACTAGCTTCAGAAAATAACAAATAGAGCAGGAGATCTAGCAG
TTGAAGTCTCCCCAGGTGCTGGATAATTGACAATAACATTTGTGATCAAAGCTGTCAAATTTTATTTT
CAAGTTCACGAAACTGCACCTGTTCCAACCATPCCCCCTTGTACACAAAATTTGATCTGCAATCAGAT
CCTTTTTACTGGGGAAGCAGCTTGGGCTTAGCAATAACTGCTACTATTTTCAATGGCAGCTTTGGTGTCT
CTGGGATCGCCATCTGCAGAACTAAATGATTGAGACAATTTTGA AAAATGGATAATGTGTTGGTCAATAT
TTTGTACAGTTTTATAAAAAACAAAATCCCCCTGCTACTGCT
```

**Fig. 10Q**

SEQ ID NO: 29

5'-AGTTCCCCGGGCTGGTATATTTATATGTTGTC-3'**Fig. 10 R**

SEQ ID NO: 30

5'-AATAGGAGCTCCATTTTCTCTCAAGATGATTAATTAATTAATTAGTC-3**Fig. 10S**

SEQ ID NO: 31

5'-AATAGGAGCTCGTAAAATGCTTCTTCGTCTCCTATTTATAATATGG-3'**Fig. 10T**

SEQ ID NO: 32

5'-  
TTACGAATTCTCCTTCCTAATTGGTGTACTATCATTTATCAAAGGGGA-3'

Fig. 11

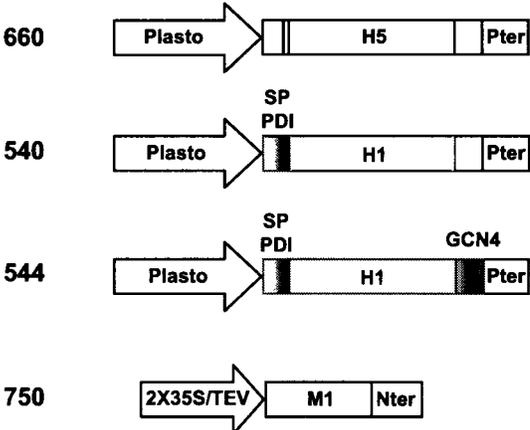
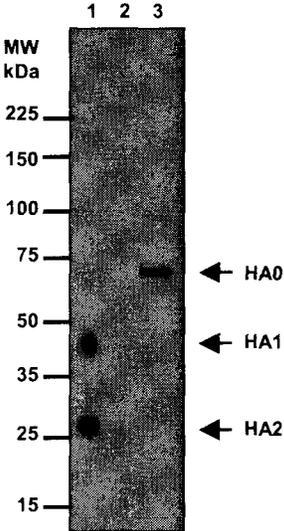


Fig. 12



- 1- Commercial H5 (A/Vietnam/1203/2004) (750 ng)
- 2- Leaf protein extract from mock (37.5  $\mu$ g)
- 3- Leaf protein extract from R660-infiltrated plant (37.5  $\mu$ g)

Fig. 13A

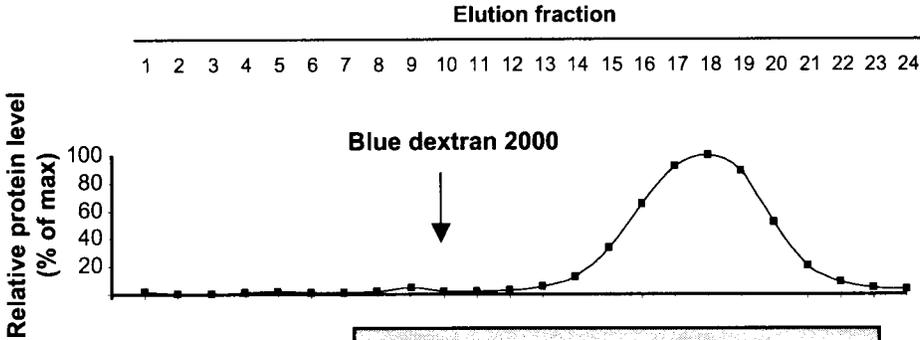


Fig. 13B

H5

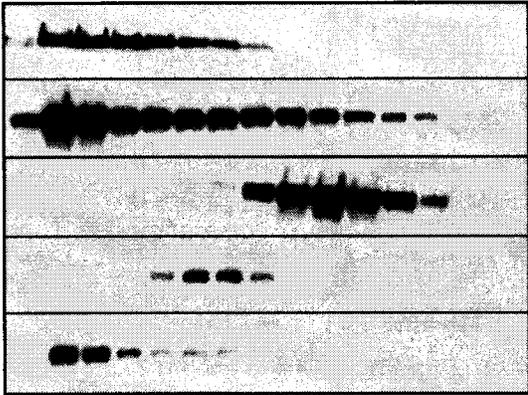


Fig. 13C

H1

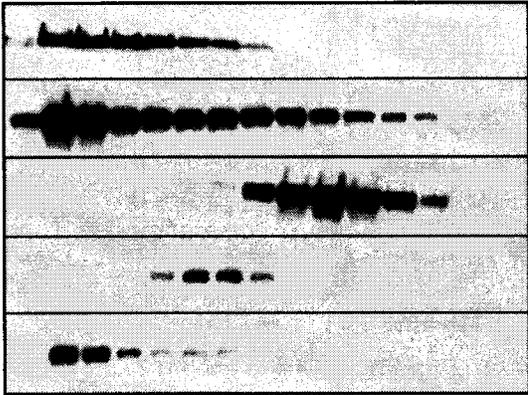


Fig. 13D

soluble H1

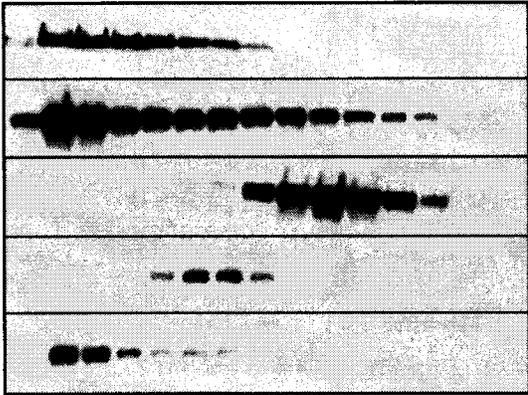


Fig. 13E

H1 rosette

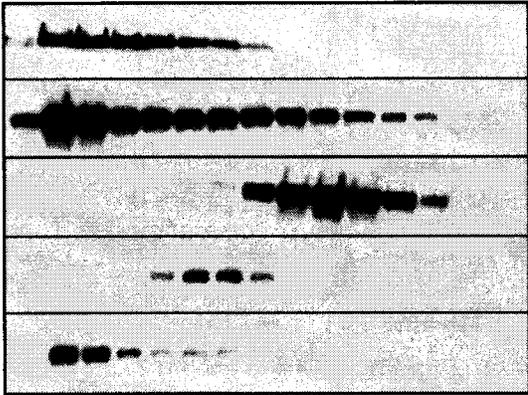


Fig. 13F

H1+M1

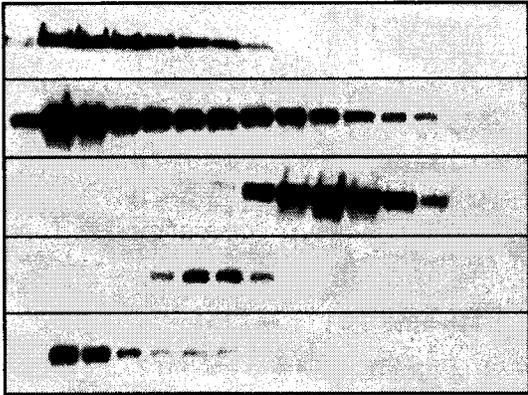


Fig.14A

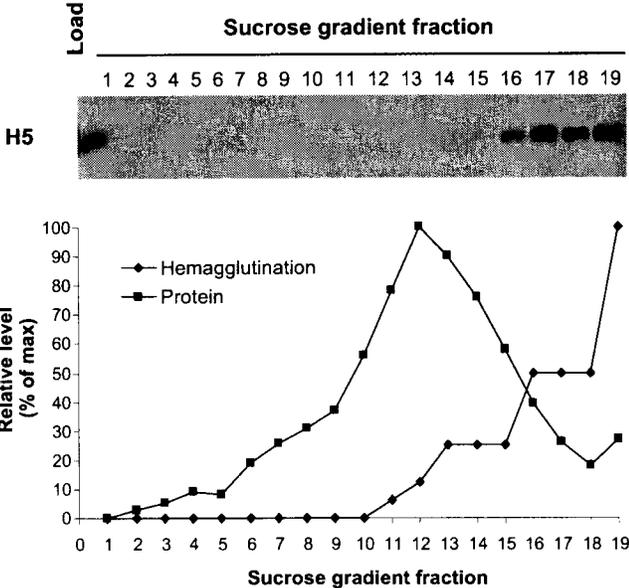


Fig. 14B

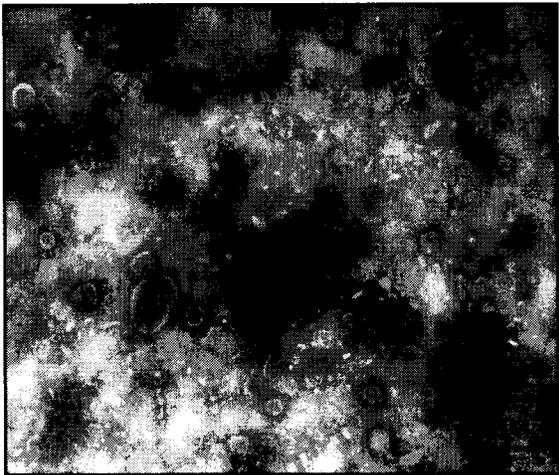


Fig. 15A

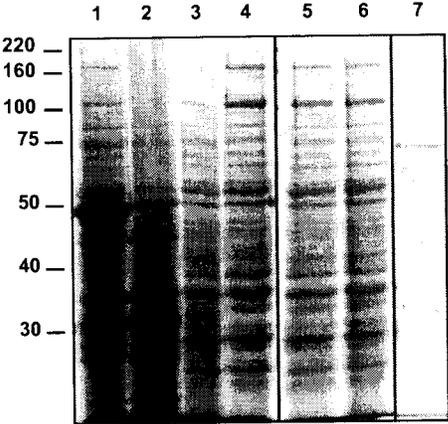


Fig. 15B

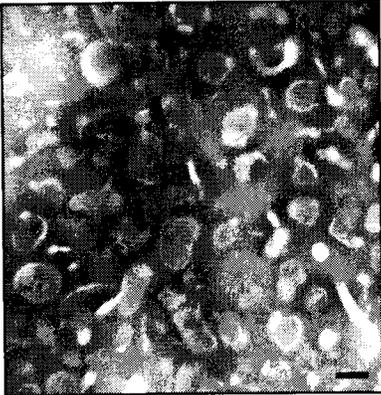


Fig. 15C



Fig. 15D

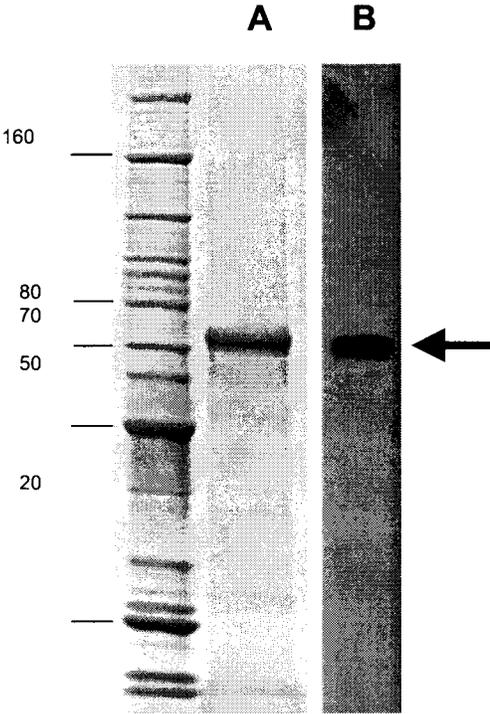


Fig. 16

SEQ ID NO: 33

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CACAATGGAAAACACTATGTCTACTAAAAGGAATAGCCCCACTACAATTGGGTAA  
TTGCAGCGTTGCCGGATGGATCTTAGGAAACCCAGAATGCGAATTACTGATTT  
CCAAGGAATCATGGTCCTACATTGTAGAAACACCAAATCCTGAGAATGGAACA  
TGTTACCCAGGGTATTTCCGCCGACTATGAGGAACTGAGGGAGCAATTGAGTTC  
AGTATCTTCATTTGAGAGATTGCAAATATTCCCCAAAGAAAGCTCATGGCCCA  
ACCACACCGTAACCGGAGTATCAGCATCATGCTCCCATAATGGGAAAAGCAGT  
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GAGCAAGTCCTATGTAAACAACAAAGAGAAAAGAAGTCCTTGTACTATGGGGTG  
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GCTTATGTCTCTGTAGTGTCTTCACATTATAGCAGAAGATTCACCCCAGAAAT  
AGCCAAAAGACCCAAAGTAAGAGATCAGGAAGGAAGAATCAACTACTACTGGA  
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GCGCCATGGTATGCTTTTGCCTGAGTAGAGGCTTTGGATCAGGAATCATCAC  
CTCAAATGCACCAATGGATGAATGTGATGCGAAGTGTCAAACACCTCAGGGAG  
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CGGGATTACAAACAAGGTGAATTCTGTAATTGAGAAAATGAACACTCAATTCA  
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GGTTCTACTGGAAAATGAAAGGACTTTGGATTTCCATGACTCCAATGTGAAGA  
ATCTGTATGAGAAAGTAAAAGCCAATTAAGAATAATGCCAAAGAAATAGGA  
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GAAAATGGAACCTTATGACTATCCAAAATATTCCGAAGAATCAAAGTTAAACA  
GGGAGAAAATTGATGGAGTGAAATTGGAATCAATGGGAGTCTATCAGATTCTG  
GCGATCTACTCAACTGTCGCCAGTTCCTGGTTCTTTTGGTCTCCCTGGGGGC  
AATCAGCTTCTGGATGTGTTCCAATGGGTCTTTGCAGTGTAGAATATGCATCT  
GAGACCAGAATTTCA

Fig. 17

## SEQ ID NO: 34

CCAAATCCTTAACATTCTTTCAACACCAACAATGGCGAAAAACGTTGCGATT  
TTCGGTTTATTGTTTTCTCTTCTTCTGTTGGTTCCTTCTCAGATCTTCGCTG  
AGGAATCATCAACTGACGCTAAGGAATTTGTTCTTACATTGGATAACACTAA  
TTTCCATGACACTGTTAAGAAGCACGATTTTCATCGTCGTTGAATTCTACGCA  
CCTTGGTGTGGACACTGTAAGAAGCTAGCCCCAGAGTATGAGAAGGCTGCTT  
CTATCTTGAGCACTCACGAGCCACCAGTTGTTTTGGCTAAAGTTGATGCCAA  
TGAGGAGCACAACAAAGACCTCGCATCGGAAAATGATGTTAAGGGATTCCCA  
ACCATTAAGATTTTTAGGAATGGTGGAAAAGCATTCAAGAATACAAAGGTC  
CCCGTGAAGCTGAAGGTATTGTTGAGTATTTGAAAAACAAAGTGGCCCTGC  
ATCCACAGAAATTAAATCTGCTGATGATGCGACCGCTTTTGTGGTGACAAC  
AAAGTTGTTATTGTCGGAGTTTTCCCTAAATTTTCTGGTGAGGAGTACGATA  
ACTTCATTGCATTAGCAGAGAAGTTGCGTCTGACTATGACTTTGCTCACAC  
TTTGAATGCCAAACACCTTCCAAAGGGAGACTCATCAGTGTCTGGGCCTGTG  
GTTAGGTTATTTAAGCCATTTGACGAGCTCTTTGTTGACTCAAAGGATTTCA  
ATGTAGAAGCTCTAGAGAAATTCATTGAAGAATCCAGTACCCCAATTGTGAC  
TGCTTCAACAATGAGCCTAGCAATCACCCTTTTGTTGTCAAATTTCTTAAAC  
TCTCCCAACGCAAAGGCTATGTTGTTTCATCAACTTTACTACCGAAGGTGCTG  
AATCTTTCAAAACAAAATACCATGAAGTGGCTGAGCAATACAAAACACAGGG  
AGTTAGCTTTCTTGTGGAGATGTTGAGTCTAGTCAAGGTGCCTTCCAGTAT  
TTTGGACTGAAGGAAGAACAAGTACCTCTAATTATTATTCAGCATAATGATG  
GCAAGAAGTTTTTCAAACCCAATTTGGAAGTTGATCAACTCCCAACTTGGTT  
GAAGGCATACAAGGATGGCAAGGTTGAACCATTTGTCAAGTCTGAACCTATT  
CCTGAAACTAACAACGAGCCTGTTAAAGTGGTGGTTGGGCAAACCTTGGAG  
ACGTTGTTTTCAAGTCTGGGAAGAATGTTTTGATAGAGTTTTATGCTCCTTG  
GTGTGGTCACTGCAAGCAGTTGGCTCCAATCTTGGATGAAGTTGCTGTCTCA  
TTCCAAAGCGATGCTGATGTTGTTATTGCAAACCTGGATGCAACTGCCAACG  
ATATCCCAACCGACACCTTTGATGTCCAAGGCTATCCAACCTTGTACTTCAG  
GTCAGCAAGTGGAAAACATCACAATACGACGGTGGTAGGACAAAGGAAGAC  
ATCATAGAATTCATTGAAAAGAACAAGGATAAAAAGTGGTCTGCTCATCAAG  
AAGTAGAACAACCAAAGCTGCTGCTCAGCCAGAAGCAGAACAACCAAAGA  
TGAGCTTTGAAAAGTTCCGCTTGGAGGATATCGGCACACAGTCATCTGCGGG  
CTTTACAACCTCTTTTGTATCTCAGAATCAGAAGTTAGGAAATCTTAGTGCCA  
ATCTATCTATTTTTGCGTTTTCATTTTATCTTTTTGGTTTACTCTAATGTATT  
ACTGAATAATGTGAGTTTTGGCGGAGTTTAGTACTGGAACTTTTGTTTCTGT  
AAAAAAAAAAAAA

**Fig. 18**

SEQ ID NO: 35

AGCGAAAGCAGGTAGATATTGAAAGATGAGTCTTCTAACCGAGGTCGAAACGTAC  
GTTCTCTCTATCATCCCCTCAGGCCCCCTCAAAGCCGAGATCGCACAGAGACTTG  
AAGATGTCTTTGCAGGGAAGAACACCGATCTTGAGGTTCTCATGGAATGGCTAAA  
GACAAGACCAATCCTGTCACCTCTGACTAAGGGGATTTTAGGATTTGTGTTACG  
CTCACCGTGCCCAGTGAGCGAGGACTGCAGCGTAGACGCTTTGTCCAAAATGCCC  
TTAATGGGAACGGGGATCCAAATAACATGGACAAAGCAGTTAAACTGTATAGGAA  
GCTCAAGAGGGGAGATAACATTCCATGGGGCCAAAGAAATCTCACTCAGTTATTCT  
GCTGGTGCACCTTGCCAGTTGTATGGGCCTCATATACAACAGGATGGGGGCTGTGA  
CCACTGAAGTGGCATTGCGCTGGTATGTGCAACCTGTGAACAGATTGCTGACTC  
CCAGCATCGGTCTCATAGGCAAATGGTGACAACAACCAACCCACTAATCAGACAT  
GAGAACAGAATGGTTTTAGCCAGCACTACAGCTAAGGCTATGGAGCAAATGGCTG  
GATCGAGTGAGCAAGCAGCAGAGGCCATGGAGGTTGCTAGTCAGGCTAGGCAAAT  
GGTGCAAGCGATGAGAACCATTGGGACTCATCCTAGCTCCAGTGCTGGTCTGAAA  
AATGATCTTCTTGAAAATTTGCAGGCCTATCAGAAACGAATGGGGGTGCAGATGC  
AACGGTTCAAGTGATCCTCTCGCTATTGCCGCAAATATCATTGGGATCTTGCACT  
TGATATTGTGGATTCTTGATCGTCTTTTTTTCAAATGCATTTACCGTCGCTTTAA  
ATACGGACTGAAAGGAGGGCCTTCTACGGAAGGAGTGCCAAAGTCTATGAGGGAA  
GAATATCGAAAGGAACAGCAGAGTGCTGTGGATGCTGACGATGGTCATTTTGTCA  
GCATAGAGCTGGAGTAAAAACTACCTTGTTTCTACT

Fig. 19

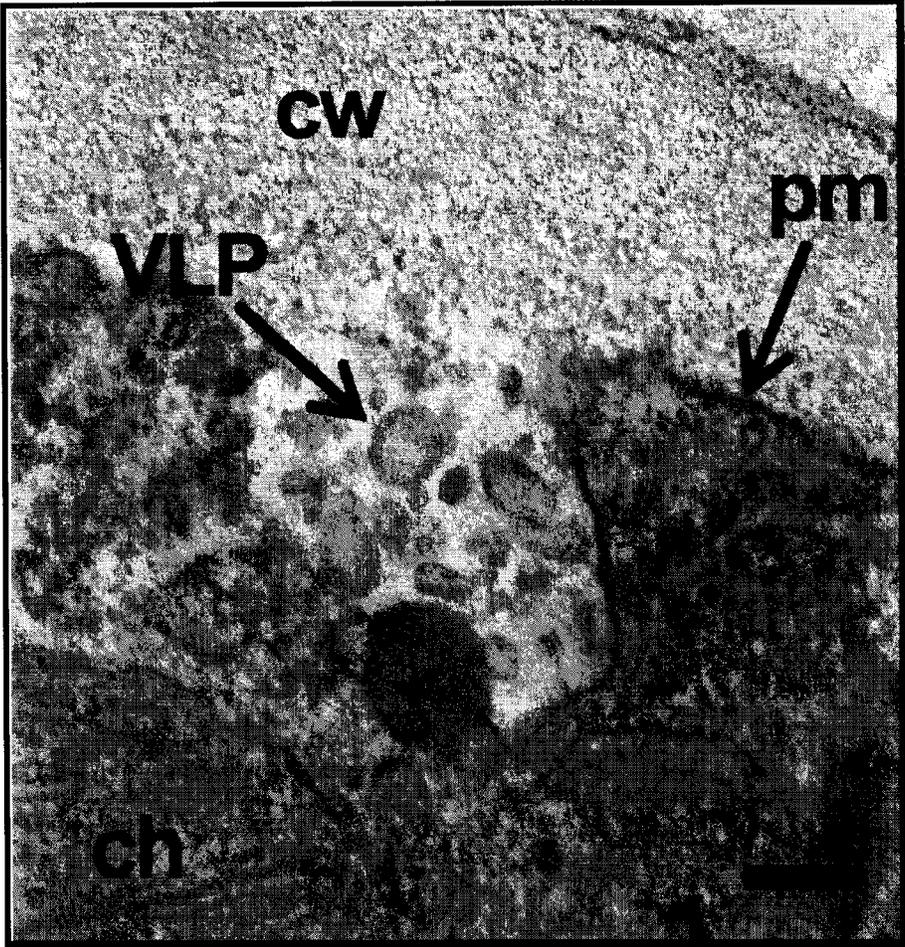


Fig. 20A

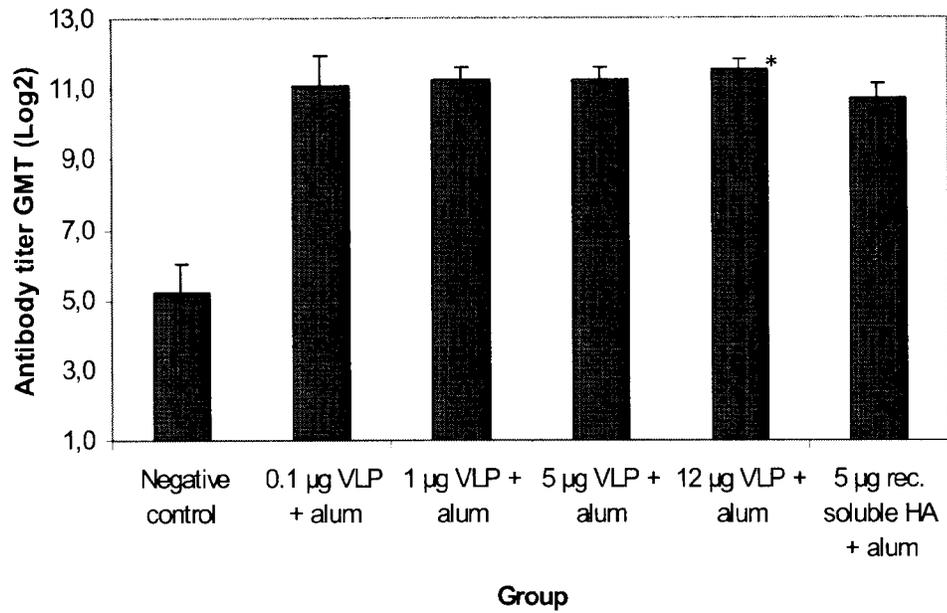


Fig. 20B

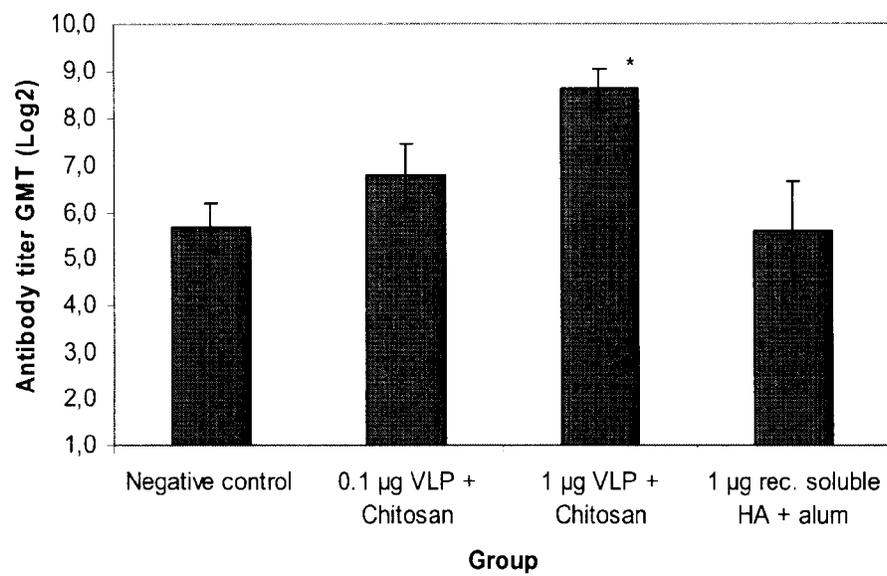


Fig. 21A

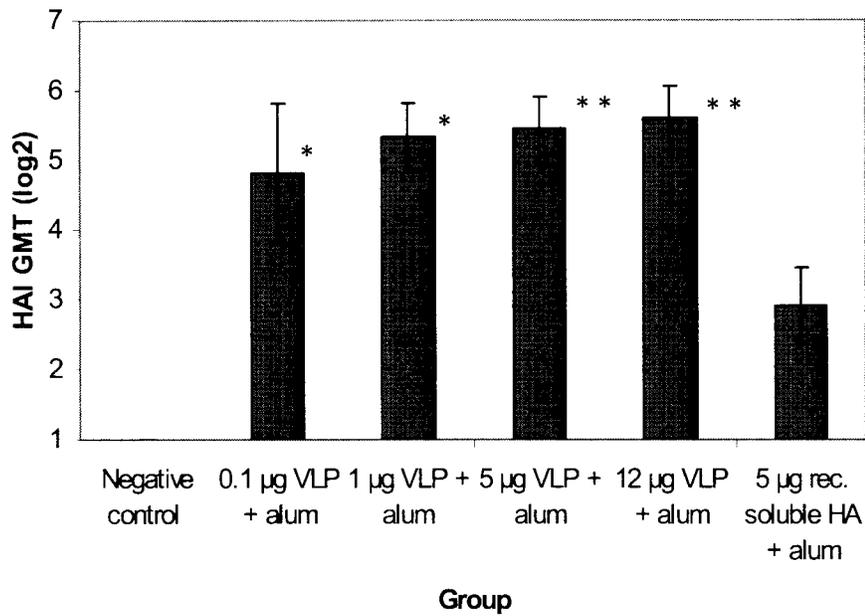


Fig. 21B

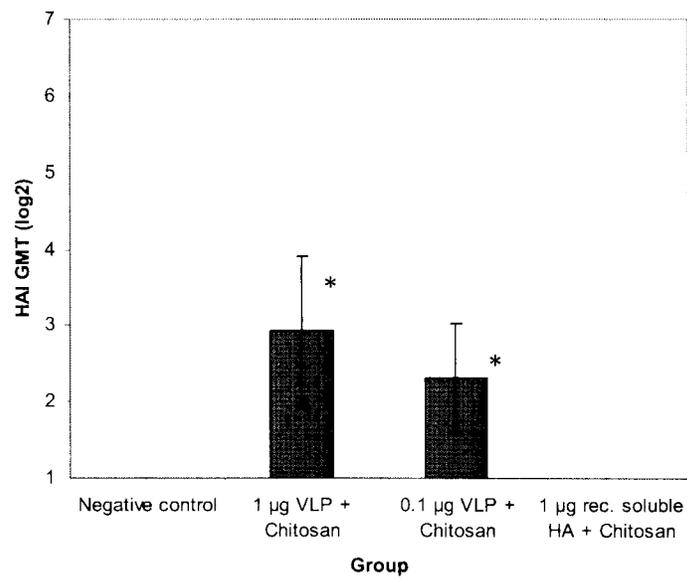


Fig. 22A

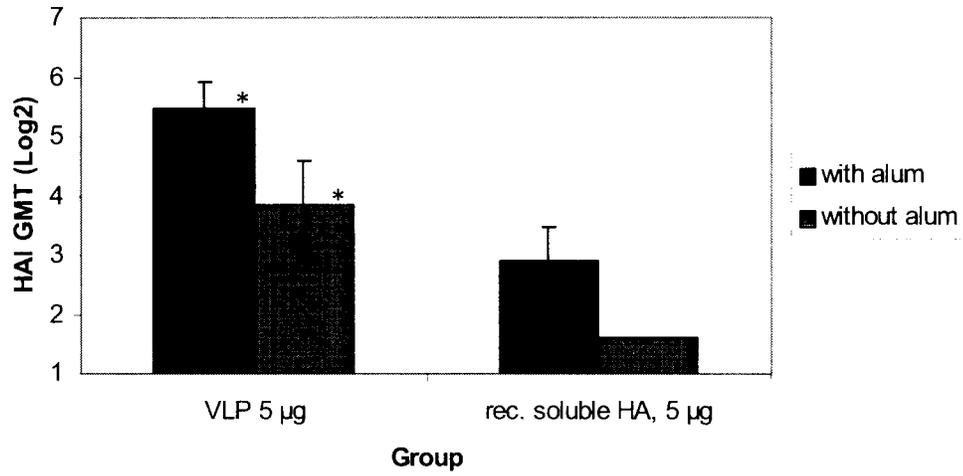


Fig. 22B

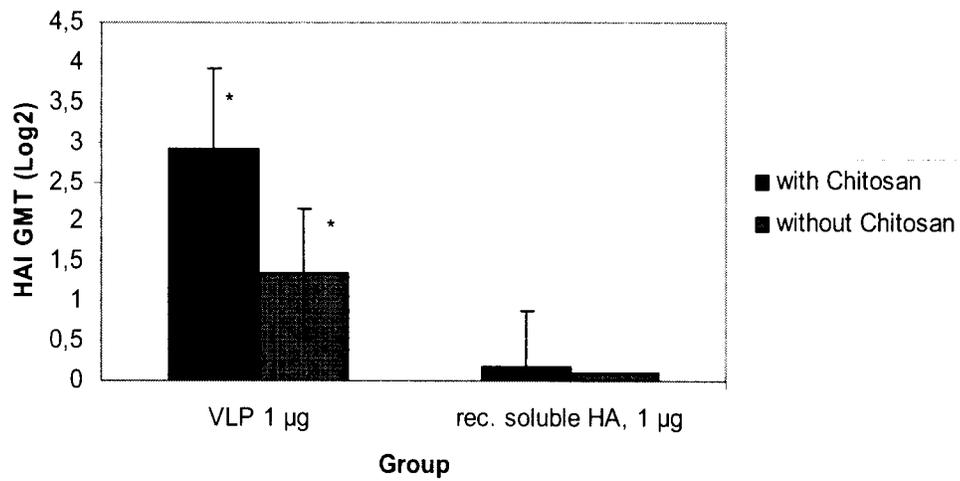


Fig. 23A

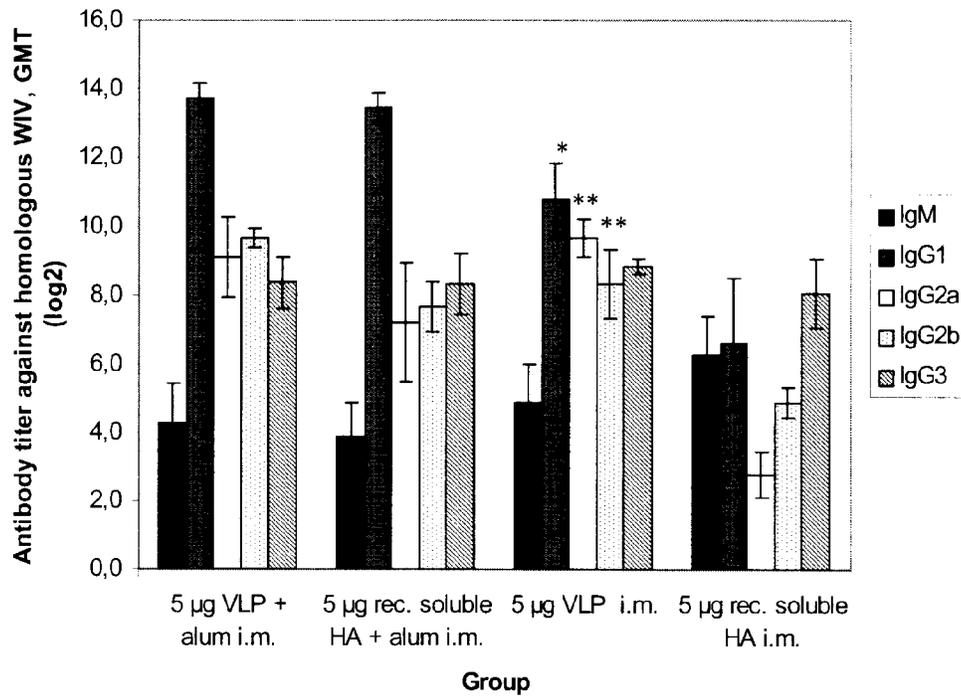


Fig. 23B

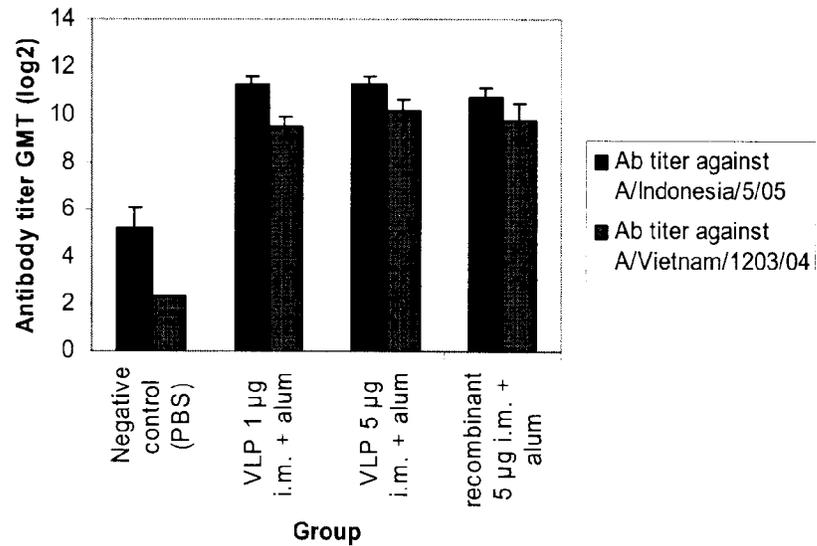


Fig. 24

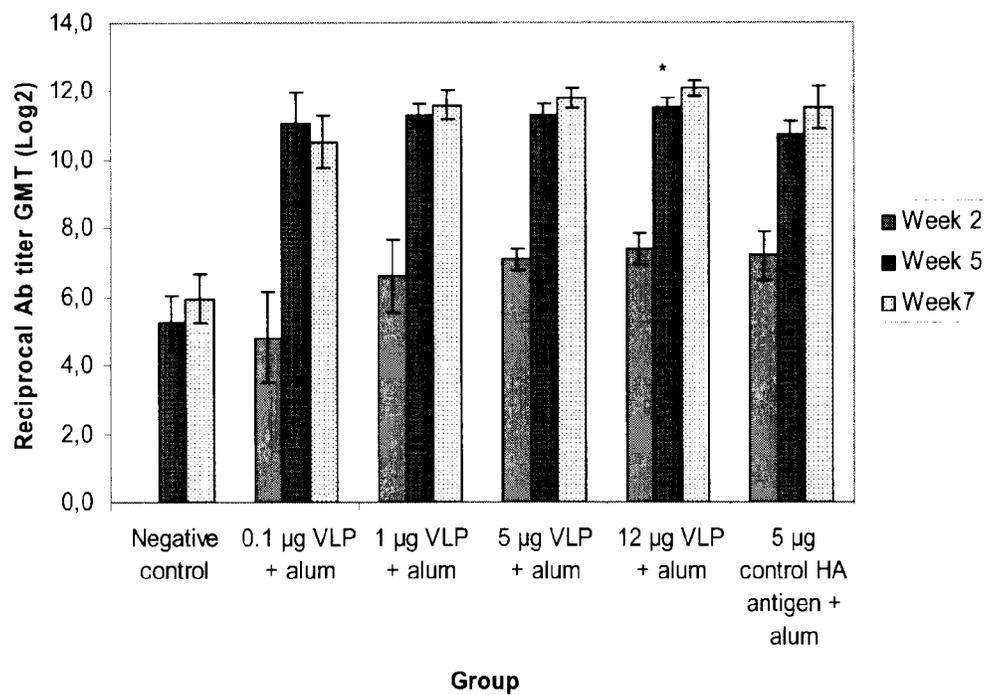


Fig. 25A

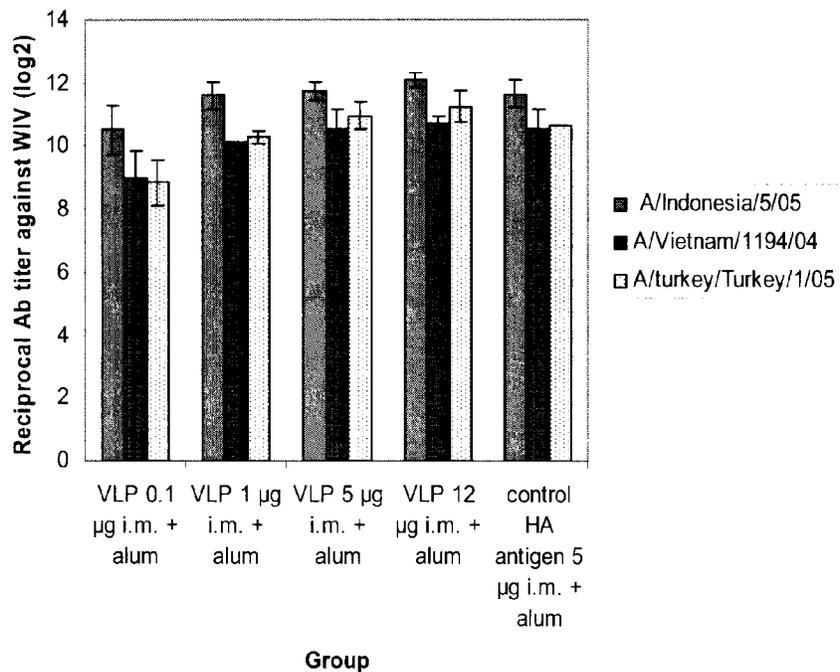
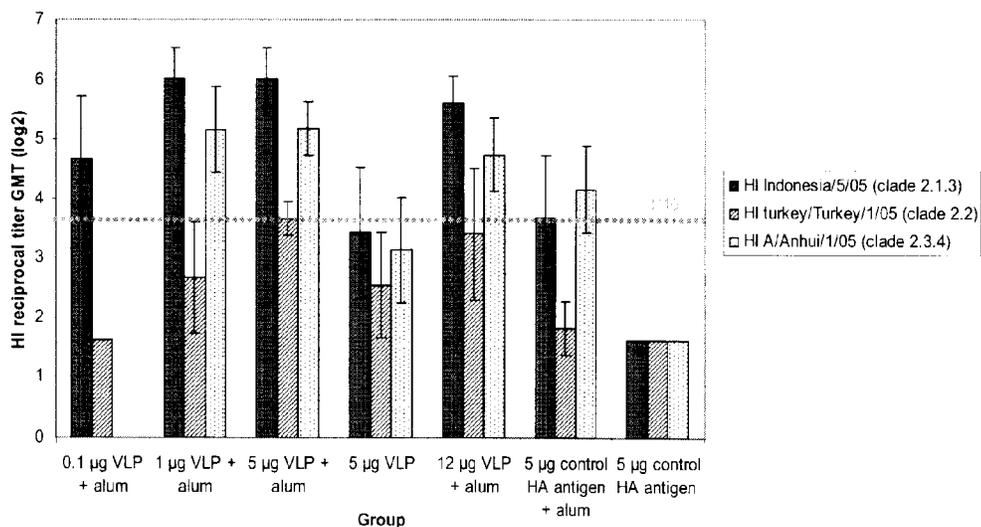


Fig. 25B



All values <10 were given an arbitrary value of 5 (1.6 in log2) and are considered negative

Fig. 26A

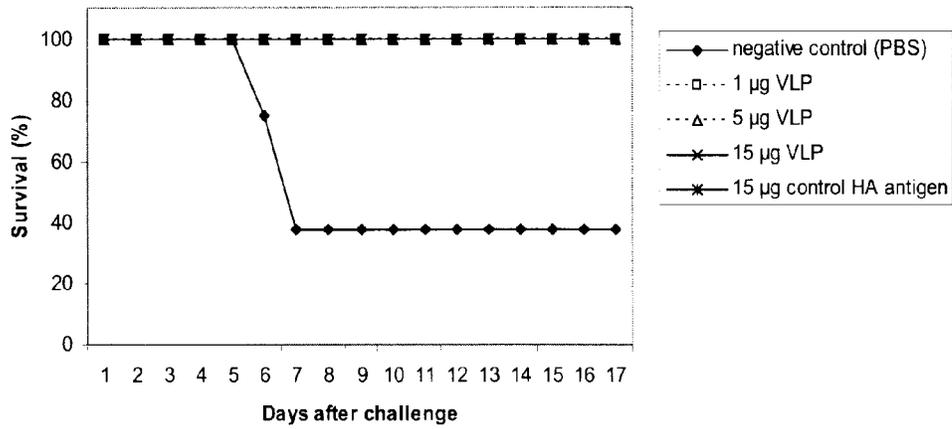


Fig. 26B

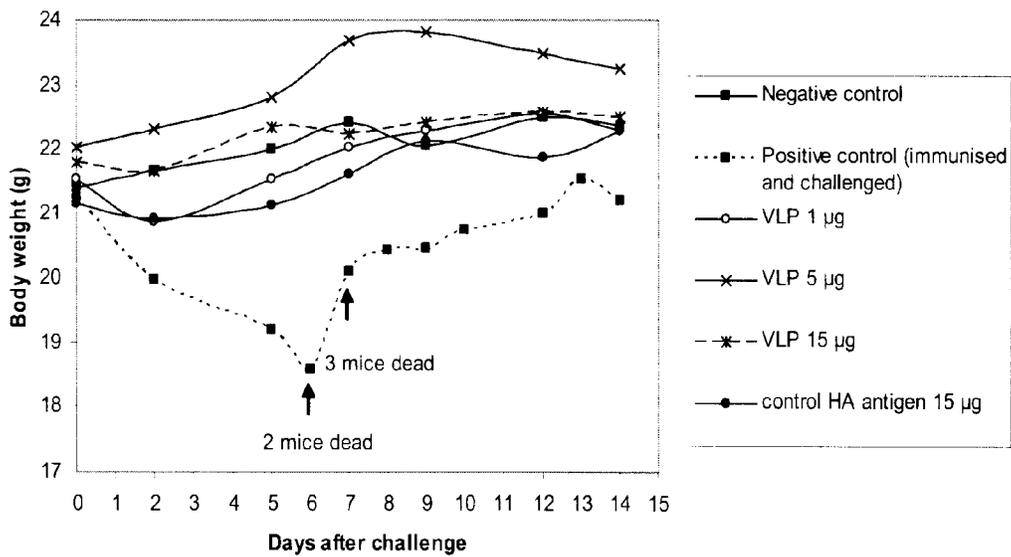
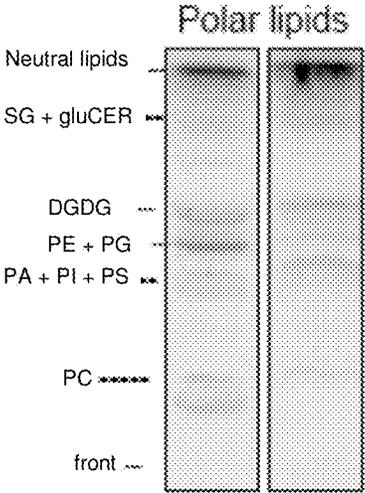
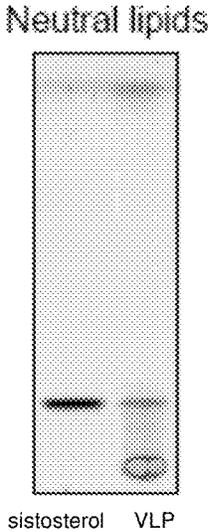


FIGURE 27

(A)



(B)



(C)

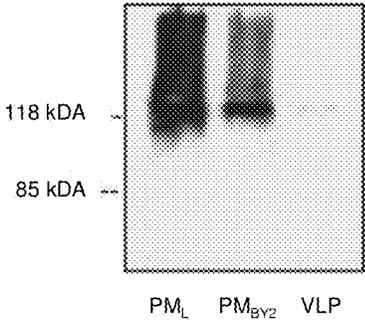


Fig. 28

SEQ ID NO: 36

CACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAAGAGAAGAGA  
CTAATTAATTAATTAATCATCTTGAGAGAAAATGAAAGTAAACTACTGGTCC  
TGTTATGCACATTTACAGCTACATATGCAGACACAATATGTATAGGCTACCAT  
GCTAACAACTCGACCGACTGTTGACACAGTACTTGAAAAGAATGTGACAG  
TGACACACTCTGTCAACCTGCTTGAGAACAGTCACAATGGAAAATATGTCT  
ATAAAAGGAATAGCCCCACTACAATTGGGTAATTGCAGCGTTGCCGGGTG  
GATCTTAGGAAACCCAGAATGCGAATTACTGATTTCCAAGGAGTCATGGTCC  
TACATTGTAGAAAACCAAATCCTGAGAATGGAACATGTTACCCAGGGCATT  
TCGCTGACTATGAGGAACTGAGGGAGCAATTGAGTTCAGTATCTTCATTTGA  
GAGGTTCGAAATATTCCCCAAAGAAAGCTCATGGCCCAACCACACCGTAACC  
GGAGTGTCAGCATCATGCTCCATAATGGGGAAAGCAGTTTTTACAGAAATT  
TGCTATGGCTGACGGGGAAGAATGGTTTGTACCCAAACCTGAGCAAGTCCT  
ATGCAAACAACAAAGAAAAAGAAGTCCTTGTACTATGGGGTGTTCATCACCC  
GCCAAACATAGGTGACCAAAGGCCCTCTATCATAACAGAAAATGCTTATGTC  
TCTGTAGTGTCTTCACATTATAGCAGAAAATTCACCCAGAAATAGCCAAAAG  
ACCCAAAGTAAGAGATCAAGAAGGAAGAATCAATTACTACTGGACTCTGCTT  
GAACCCGGGGATACAATAATATTTGAGGCAAATGGAAATCTAATAGCGCCAA  
GATATGCTTTCGCACTGAGTAGAGGCTTTGGATCAGGAATCATCAACTCAA  
TGCACCAATGGATAAATGTGATGCGAAGTGCCAAACACCTCAGGGAGCTATA  
AACAGCAGTCTTCCTTCCAGAACGTACACCCAGTCACAATAGGAGAGTGTC  
CAAAGTATGTCAGGAGTGCAAAATTAAGGATGGTTACAGGACTAAGGAACAT  
CCCATCCATTCAATCCAGAGGTTTGGTTGGAGCCATTGCCGGTTTCATTGAA  
GGGGGGTGGACTGGAATGGTAGATGGTTGGTATGGTTATCATCATCAGAAT  
GAGCAAGGATCTGGCTATGCTGCAGATCAAAAAAGCACACAAAATGCCATTA  
ATGGGATTACAAACAAGGTCAATTCTGTAATTGAGAAAATGAACACTCAATTC  
ACAGCAGTGGGCAAAGAGTTCAACAAATTGGAAAGAAGGATGGAAAATTTG  
AATAAAAAAGTTGATGATGGGTTTATAGACATTTGGACATATAATGCAGAACT  
GTTGGTTCTACTGGAAAATGAAAGGACTTTGGATTTCCATGACTCCAATGTG  
AAGAATCTGTATGAGAAAGTAAAAAGCCAGTTAAAGAATAATGCTAAAGAAAT  
AGGAAATGGGTGTTTTGAGTTCTATCACAAGTGTAAACGATGAATGCATGGAG  
AGTGTAAGAATGGAACCTTATGACTATCCAAAATATTCCGAAGAATCAAAGTT  
AACAGGGAGAAAATTGATGGAGTGAAATTGGAATCAATGGGAGTCTATCAG  
ATTCTGGCGATCTACTCAACAGTCGCCAGTTCTCTGGTTCTTTTGGTCTCCC  
TGGGGGCAATCAGCTTCTGGATGTGTTCCAATGGGTCTTTACAGTGTAAGAAT  
ATGCATCTAAGAGCTC

Fig. 29

SEQ ID NO: 37

CACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAAGAGAAGAGACT  
AATTAATTAATTAATCATCTTGAGAGAAAATGAAAGTAAACTACTGGTCCTGTTA  
TGCACATTTACAGCTACATATGCAGACACAATATGTATAGGCTACCATGCCAACA  
ACTCAACCGACACTGTTGACACAGTACTTGAGAAGAATGTGACAGTGACACACT  
CTGTCAACCTGCTTGAGGACAGTCACAATGGAAAATTATGTCTATTAAGGAAT  
AGCCCCACTACAATTGGGTAATTGCAGCGTTGCCGGATGGATCTTAGGAAACCC  
AGAATGCGAATTAAGTATTCCAGGGAATCATGGTCCTACATTGTAGAAAAACCA  
AATCCTGAGAATGGAACATGTTACCCAGGGCATTTCGCCGACTATGAGGAACTG  
AGGGAGCAATTGAGTTCAGTATCTTCATTTGAGAGATTGCAAATATCCCAAAG  
AAAGCTCATGGCCCAACCACACCACAACCGGAGTATCAGCATCATGCTCCCAT  
ATGGGGAAAGCAGTTTTTACAAAAATTTGCTATGGCTGACGGGGGAAGAATGGTTT  
GTACCCAAACCTGAGCAAGTCCTATGCAAACAACAAAGAGAAAGAAGTCCTTGTA  
CTATGGGGTGTTCATCACCCGCCTAACATAGGTGACCAAAGGGCTCTCTATCAT  
AAAGAAAATGCTTATGTCTCTGTAGTGTCTTCACATTATAGCAGAAAATTCACCCC  
AGAAATAGCCAAAAGACCCAAAGTAAGAGATCAAGAAGGAAGAATCAACTACTAC  
TGGACTCTACTTGAACCCGGGGATACAATAATTTGAGGCAAATGGAATCTAA  
TAGCGCCAAGATATGCTTTCGCACTGAGTAGAGGCTTTGGATCAGGAATCATCA  
ACTCAAATGCACCAATGGATGAATGTGATGCCAAGTGCCAAACACCTCAGGGAG  
CTATAAACAGCAGTCTTCCTTTCCAGAATGTACACCCTGTCACAATAGGAGAGTG  
TCCAAAGTATGTCAGGAGTGCAAAATTAAGGATGGTTACAGGACTAAGGAACAT  
CCCATCCATTCAATCCAGAGGTTTGTGGAGCCATTGCCGGTTTCATTGAAGG  
GGGGTGGACTGGAATGGTAGATGGTTGGTATGGTTATCATCATCAGAATGAGCA  
AGGATCTGGCTATGCTGCAGATCAAAAAGCACACAAAATGCCATTAATGGGATT  
ACAAACAAGGTCAATTCTGTAATTGAGAAAATGAACACTCAATTCACAGCTGTGG  
GCAAAGAGTTCAACAAATTGGAAAGAAGGATGGAAACTTAAATAAAAAAGTTGA  
TGATGGGTTTATAGACATTTGGACATATAATGCAGAATTGTTGGTTCTACTGGAA  
AATGAAAGGACTTTGGATTTCCATGACTCCAATGTGAAGAATCTGTATGAGAAAG  
TAAAAAGCCAATTAAGAATAATGCCAAAGAAATAGGAAATGGGTGTTTTGAGTT  
CTATCATAAGTGTAACGATGAATGCATGGAGAGTGTA AAAAATGGAECTTATGAC  
TATCCAAAATATCCGAAGAATCAAAGTTAAACAGGGAGAAAATTGATGGAGTGA  
AATTGGAATCAATGGGAGTCTATCAGATTCTGGCGATCTACTCAACAGTCGCCAG  
TTCTCTGGTTCTTTTGGTCTCCCTGGGGGCAATCAGCTTCTGGATGTGTTCCAAT  
GGGTCTTTCAGTGTAGAATATGCATCTGAGAGCTC

Fig. 30

SEQ ID NO: 38

CACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAAGAGAAGAGA  
CTAATTAATTAATTAATCATCTTGAGAGAAAATGAAGACTATCATTGCTTTGAG  
CTACATTCTATGTCTGGTTTTCACTCAAAAACTTCCCGGAAATGACAACAGCA  
CGGCAACGCTGTGCCTTGGGCACCATGCAGTACCAAACGGAACGATAGTGA  
AAACAATCACGAATGACCAAATTGAAGTTACTAATGCTACTGAGCTGGTTTCAG  
AGTTCCTCAACAGGTGAAATATGCGACAGTCCTCATCAGATCCTTGATGGAG  
AAAACTGCACACTAATAGATGCTCTATTGGGAGACCCTCAGTGTGATGGCTT  
CCAAAATAAGAAATGGGACCTTTTTGTTGAACGCAGCAAAGCCTACAGCAACT  
GTTACCCTTATGATGTGCCGGATTATGCCTCCCTTAGGTCACTAGTTGCCTCA  
TCCGGCACACTGGAGTTTAAACAATGAAAGTTTCAATTGGACTGGAGTCACTCA  
AAACGGAACAAGCTCTGCTTGCATAAGGAGATCTAATAACAGTTTCTTTAGTA  
GATTGAATTGGTTGACCCACTTAAAATTCAAATACCCAGCATTGAACGTGACT  
ATGCCAAACAATGAAAAATTTGACAAATTGTACATTTGGGGGGTTCCACCACC  
GGGTACGGACAATGACCAAATCTTCCTGTATGCTCAAGCATCAGGAAGAATC  
ACAGTCTCTACCAAAGAAGCCAACAAACTGTAATCCCGAATATCGGATCTAG  
ACCCAGAGTAAGGAATATCCCCAGCAGAATAAGCATCTATTGGACAATAGTAA  
AACCGGGAGACATACTTTTGATTAACAGCACAGGGAATCTAATTGCTCCTAG  
GGGTTACTTCAAATACGAAGTGGGAAAAGCTCAATAATGAGATCAGATGCA  
CCCATTGGCAAATGCAATTCTGAATGCATCACTCCAAACGGAAGCATTCCCAA  
TGACAAACCATTCCAAAATGTAACAGGATCACATACGGGGCCTGTCCCAGA  
TATGTTAAGCAAAACACTCTGAAATTGGCAACAGGGATGCGAAATGTACCAG  
AGAAACAAACTAGAGGCATATTTGGCGCAATCGCGGGTTTCATAGAAAATGG  
TTGGGAGGGAATGGTGGATGGTTGGTATGGTTTCAGGCATCAAATTCTGAG  
GGAATAGGACAAGCAGCAGATCTCAAAGCACTCAAGCAGCAATCGATCAAA  
TCAATGGGAAGCTGAATAGTTGATCGGGAAAACCAACGAGAAATCCATCA  
GATTGAAAAAGAGTTCTCAGAAGTCGAAGGGAGAATCCAGGACCTTGAGAAA  
TATGTTGAGGACACCAAATAGATCTCTGGTCATACAACGCGGAGCTTCTTGT  
TGCCCTGGAGAACCAACATACAATTGATCTAACTGACTCAGAAATGAACAAAC  
TGTTTGAAAAACAAAGAAGCAACTGAGGGAAAATGCTGAGGATATGGGCAA  
TGGTTGTTTCAAATATACCACAAATGTGACAATGCCTGCATAGGATCAATCA  
GAAATGGAACTTATGACCACGATGTATACAGAGATGAAGCATTAAACAACCG  
GTTCCAGATCAAGGGCGTTGAGCTGAAGTCAGGATACAAAGATTGGATACTA  
TGGATTTCTTTGCCATATCATGTTTTTGCCTTGTGTTGCTTTGTTGGGGTTC  
ATCATGTGGGCCTGCCAAAAGGCAACATTAGGTGCAACATTTGCATTTGAG  
AGCTC

Fig. 31

SEQ ID NO: 39

CACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAAGAGAAGAG  
ACTAATTAATTAATTAATCATCTTGAGAGAAAATGAAGACTATCATTGCTTTG  
AGCTACATTCTATGTCTGGTTTTCACTCAAAAACCTCCCGGAAATGACAACA  
GCACGGCAACGCTGTGCCTTGGGCACCATGCAGTACCAAACGGAACGATA  
GTGAAAACAATCACGAATGACCAAATTGAAGTTACTAATGCTACTGAGCTG  
GTTCAAGAGTTCCCTCAACAGGTGGAATATGCGACAGTCCTCATCAGATCCTT  
GATGGAGAAAACCTGCACACTAATAGATGCTCTATTGGGAGACCCTCAGTGT  
GATGGCTTCCAAAATAAGAAATGGGACCTTTTTGTTGAACGCAGCAAAGCC  
TACAGCAACTGTTACCCTTATGATGTGCCGGATTATGCCTCCCTTAGGTCA  
CTAGTTGCCTCATCCGGCACACTGGAGTTTAAACGATGAAAGTTTCAATTGG  
ACTGGAGTCACTCAAAATGGAACAAGCTCTGCTTGCAAAGGAGATCTAAT  
AACAGTTTCTTTAGTAGATTGAATTGGTTGACCCACTTAAAATTCAAATACC  
CAGCATTGAACGTGACTATGCCAAACAATGAAAAATTTGACAAATTGTACAT  
TTGGGGGGTTCACCACCCGGGTACGGACAATGACCAAATCTTCCTGCATG  
CTCAAGCATCAGGAAGAATCACAGTCTCTACCAAAGAAGCCAACAAACTG  
TAATCCCGAATATCGGATCTAGACCCAGAATAAGGAATATCCCCAGCAGAA  
TAAGCATCTATTGGACAATAGTAAAACCGGGAGACATACTTTTGATTAACAG  
CACAGGGAATCTAATTGCTCCTAGGGGTTACTTCAAATACGAAGTGGGAA  
AAGCTCAATAATGAGATCAGATGCACCCATTGGCAAATGCAATTCTGAATG  
CATCACTCCAAATGGAAGCATTCCCAATGACAAACCATTTCAAATGTAAAC  
AGGATCACATATGGGGCCTGTCCAGATATGTTAAGCAAACACTCTGAAA  
TTGGCAACAGGGATGCGAAATGTACCAGAGAAACAACTAGAGGCATATTT  
GGCGCAATCGCGGGTTTCATAGAAAATGGTTGGGAGGGAATGGTGGATGG  
TTGGTACGGTTTCAGGCATCAAATTTCTGAGGGAATAGGACAAGCAGCAGA  
TCTCAAAGCACTCAAGCAGCAATCAATCAAATCAATGGGAAGCTGAATAG  
GTTGATCGGGAAAACCAACGAGAAATTCCATCAGATTGAAAAAGAGTTCTC  
AGAAGTAGAAGGGAGAATCCAGGACCTCGAGAAATATGTTGAGGACACTAA  
AATAGATCTCTGGTCATACAACGCGGAGCTTCTTGTGGCCCTGGAGAACCA  
ACATACAATTGATCTAACTGACTCAGAAATGAACAACTGTTTGAAAGAACA  
AAGAAGCAACTGAGGGAAAATGCTGAGGATATGGGCAATGGTTGTTTCAA  
ATATACCACAAATGTGACAATGCCTGCATAGGATCAATCAGAAATGGAACCTT  
ATGACCATGATGTATACAGAGATGAAGCATTAAACAACCGGTTCCAGATCA  
AAGGCGTTGAGCTGAAGTCAGGATACAAAGATTGGATACTATGGATTTCTT  
TTGCCATATCATGTTTTTTGCTTTGTGTTGCTTTGTTGGGGTTCATCATGTG  
GGCTGCCAAAAGGCAACATTAGGTGCAACATTTGCATTTGAGAGCTC

Fig. 32

SEQ ID NO: 40

CACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAAGAGAAGA  
GACTAATTAATTAATTAATCATCTTGAGAGAAAATGAAGGCAATAATTGTAC  
TACTCATGGTAGTAACATCCAATGCAGATCGAATCTGCACTGGGATAACAT  
CGTCAAACCTCACCACATGTTGTCAAACCTGCTACTCAAGGGGAGGTCAAT  
GTGACTGGTGTAAATACCACTGACAACAACCCACCAAATCTCATTTTGCA  
AATCTCAAAGGAACAGAAACCAGAGGGAAACTATGCCCAAATGCCTCAA  
CTGCACAGATCTGGACGTGGCCTTGGGCAGACCAAATGCACGGGGAAC  
ATACCCTCGGCAAGAGTTTCAATACTCCATGAAGTCAGACCTGTTACATCT  
GGGTGCTTTCCTATAATGCACGACAGAACAAAAATTAGACAGCTGCCTAAA  
CTTCTCAGAGGATACGAACATATCAGGTTATCAACTCATAACGTTATCAAT  
GCAGAAAATGCACCAGGAGGACCCTACAAAATTGGAACCTCAGGGTCTTG  
CCCTAACGTTACCAATGGAAACGGATTTTTCGCAACAATGGCTTGGGCCG  
TCCCAAAAAACGACAACAACAAAACAGCAACAATTCATTAACAATAGAAG  
TACCATACATTTGTACAGAAGGAGAAGACCAAATTACCGTTTGGGGGTTT  
CACTCTGATAACGAAACCCAAATGGCAAAGCTCTATGGGGACTCAAAGCC  
CCAGAAGTTCACCTCATCTGCCAACGGAGTGACCACACATTACGTTTCAC  
AGATTGGTGGCTTCCCAAATCAAACAGAAGACGGAGGACTACCACAAAGC  
GGTAGAATTGTTGTTGATTACATGGTGCAAAAATCTGGGAAAACAGGAAC  
AATTACCTATCAAAGAGGTATTTTATTGCCTCAAAAAGTGTGGTGCGCAAG  
TGGCAGGAGCAAGGTAATAAAAGGATCGTTGCCTTTAATTGGAGAAGCAG  
ATTGCCTCCACGAAAAATACGGTGGATTAACAACAAGCAAGCCTTACTACA  
CAGGGGAACATGCAAAGGCCATAGGAAATTGCCCAATATGGGTGAAAACA  
CCCTTGAAGCTGGCCAATGGAACCAAATATAGACCTCCTGCAAAACTATTA  
AAGGAAAGGGGTTTCTTCGGAGCTATTGCTGGTTTCTTAGAAGGAGGATG  
GGAAGGAATGATTGCAGGTTGGCACGGATACACATCCCATGGGGCACAT  
GGAGTAGCGGTGGCAGCAGACCTTAAGAGCACTCAAGAGGCCATAAACA  
AGATAACAAAAAATCTCAACTCTTTGAGTGAGCTGGAAGTAAAGAATCTTC  
AAAGACTAAGCGGTGCCATGGATGAACTCCACAACGAAATACTAGAACTA  
GACGAGAAAGTGGATGATCTCAGAGCTGATACAATAAGCTCACAAATAGA  
ACTCGCAGTCCTGCTTTC CAATGAAGGAATAATAAACAGTGAAGATGAGC  
ATCTCTTGGCGCTTGAAAGAAAGCTGAAGAAAATGCTGGGCCCTCTGCT  
GTAGAGATAGGGAATGGATGCTTTGAAACCAAACACAAGTGCAACCAGAC  
CTGTCTCGACAGAATAGCTGCTGGTACCTTTGATGCAGGAGAATTTTCTCT  
CCCCACTTTTGATTCACTGAATATACTGCTGCATCTTTAAATGACGATGG  
ATTGGATAATCATACTATACTGCTTTACTACTCAACTGCTGCCTCCAGTTT  
GGCTGTAACATTGATGATAGCTATCTTTGTTGTTTATATGGTCTCCAGAGA  
CAATGTTTCTTGCTCCATCTGTCTATAAGAGCTC

Fig. 33

SEQ ID NO: 41

CACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAAGAGAA  
GAGACTAATTAATTAATTAATCATCTTGAGAGAAAATGAAGGCAATAATT  
GTACTACTCATGGTAGTAACATCCAATGCAGATCGAATCTGCACTGGAA  
TAACATCTTCAAACCTCACCTCATGTGGTCAAACAGCCACTCAAGGGGA  
GGTCAATGTGACTGGTGTGATACCACTAACAACAACCAACAAAATCT  
TATTTTGCAAATCTCAAAGGAACAAGGACCAGAGGGAACTATGCCCA  
GACTGTCTCAACTGCACAGATCTGGATGTGGCTTTGGGCAGACCAATG  
TGTGTGGGGACCACACCTTCGGCGAAGGCTTCAATACTCCACGAAGTC  
AAACCTGTTACATCCGGGTGCTTTCCTATAATGCACGACAGAACAAAA  
TCAGGCAACTACCCAATCTTCTCAGAGGATATGAAAATATCAGGCTATC  
AACCCAAAACGTCATCGATGCGGAAAAGGCACCAGGAGGACCCTACA  
GACTTGGAACCTCAGGATCTTGCCCTAACGCTACCAGTAAGAGCGGAT  
TTTTCGCAACAATGGCTTGGGCTGTCCCAAAGGACAACAACAAAATG  
CAACGAACCCACTAACAGTAGAAGTACCATACATTTGTACAGAAGGGG  
AAGACCAAATCACTGTTTGGGGTTCCATTGAGATAACAAAACCCAAAT  
GAAGAACCTCTATGGAGACTCAAATCCTCAAAGTTCACCTCATCTGCT  
AATGGAGTAACCACACACTATGTTTCTCAGATTGGCAGCTTCCCAGATC  
AAACAGAAGACGGAGGACTACCACAAAGCGGCAGGATTGTTGTTGATT  
ACATGATGCAAAAACCTGGGAAAACAGGAACAATTGTCTACCAAAGAG  
GTGTTTTGTTGCCTCAAAGGTGTGGTGC GCGAGTGGCAGGAGCAAA  
GTAATAAAAGGGTCCTTGCCTTAATTGGTGAAGCAGATTGCCTTCATG  
AAAATACGGTGGATTAAACAAAAGCAAGCCTTACTACACAGGAGAACA  
TGCAAAGCCATAGGAAATTGCCAATATGGGTGAAAACACCTTTGAA  
GCTCGCCAATGGAACCAAATATAGACCTCCTGCAAACTATTAAGGAA  
AGGGGTTTCTTCGGAGCTATTGCTGGTTTCTAGAAAGGAGGATGGGAA  
GGAATGATTGCAGGCTGGCACGGATACACATCTCACGGAGCACATGG  
AGTGGCAGTGGCGGCGGACCTTAAGAGTACGCAAGAAGCTATAAACAA  
GATAACAAAAAATCTCAATTCTTTGAGTGAGCTAGAAGTAAAGAATCTT  
CAAAGACTAAGTGGTGCCATGGATGAACTCCACAACGAAATACTCGAG  
CTGGATGAGAAAGTGGATGATCTCAGAGCTGACACTATAAGCTCGCAA  
ATAGAACTTGCAGTCTTGCTTCCAACGAAGGAATAATAACAGTGAAG  
ATGAGCATCTATTGGCACTTGAGAGAAAATAAGAAAATGCTGGGTC  
CCTCTGCTGTAGAGATAGGAAATGGATGCTTCGAAACCAACACAAGT  
GCAACCAGACCTGCTTAGACAGGATAGCTGCTGGCACCTTTAATGCAG  
GAGAATTTTCTCTCCCCACTTTTGATTCACTGAACATTACTGCTGCATCT  
TTAAATGATGATGGATTGGATAACCATACTATACTGCTCTATTACTCAAC  
TGCTGCTTCTAGTTTGGCTGTAACATTGATGCTAGCTATTTTTATTGTT  
ATATGGTCTCCAGAGACAACGTTTCATGCTCCATCTGTCTATAAGAGCT  
C

Fig. 34

SEQ ID NO: 42

CACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAAGAGAA  
GAGACTAATTAATTAATTAATCATCTTGAGAGAAAATGGCCATCATTTA  
TCTAATTCTCCTGTTACAGCAGTGAGAGGGGACCAAATATGCATTGG  
ATACCATGCCAATAATTCCACAGAGAAGGTCGACACAATTCTAGAGCG  
GAACGTCACTGTGACTCATGCCAAGGACATTCTTGAGAAGACCCATAA  
CGGAAAGTTATGCAAACCTAAACGGAATCCCTCCACTTGAAGTAGGGGA  
CTGTAGCATTGCCGGATGGCTCCTTGAAATCCAGAATGTGATAGGCT  
TCTAAGTGTGCCAGAATGGTCCTATATAATGGAGAAAGAAAACCCGAG  
AGACGGTTTGTGTTATCCAGGCAGCTTCAATGATTATGAAGAATTGAAA  
CATCTCCTCAGCAGCGTGAAACATTTGAGAAAGTAAAGATTCTGCC  
AAAGATAGATGGACACAGCATAACAACCTGGAGGTTACGGGCCTG  
CGCGGTGTCTGGTAATCCATCATTCTTCAGGAACATGGTCTGGCTGAC  
AAAGAAAGAATCAAATTATCCGGTTGCCAAAGGATCGTACAACAATAC  
AAGCGGAGAACAATGCTAATAATTTGGGGGGTGCACCATCCCAATGA  
TGAGACAGAACAAGAACATTGTACCAGAATGTGGGAACCTATGTTTC  
CGTAGGCACATCAACATTGAACAAAAGGTCAACCCCAGACATAGCAAC  
AAGGCCATAAGTGAATGGACTAGGAAGTAGAATGGAGTTCTCTTGGAC  
CCTATTGGATATGTGGGACACCATAAATTTTGAGAGTACTGGTAATCTA  
ATTGCACCAGAGTATGGATTCAAATATCGAAAAGAGGTAGTTCAGGG  
ATCATGAAAACAGAAGGAACACTTGAGAACTGTGAGACCAAATGCCAA  
ACTCCTTTGGGAGCAATAAATAACAATTGCCTTTTCACAATGTCCACC  
CACTGACAATAGGTGAGTGCCCCAATATGTAAAATCGGAGAAGTTGG  
TCTTAGCAACAGGACTAAGGAATGTTCCCCAGATTGAATCAAGAGGAT  
TGTTTGGGGCAATAGCTGGTTTTATAGAAGGAGGATGGCAAGGAATG  
GTTGATGGTTGGTATGGATACCATCACAGCAATGACCAGGGATCAGG  
GTATGCAGCAGACAAAGAATCCACTCAAAGGCATTTGATGGAATCAC  
CAACAAGGTAAATTCTGTGATTGAAAAGATGAACACCCAATTTGAAGCT  
GTTGGGAAAGAGTTCAGTAACTTAGAGAGAAGACTGGAGAACTTGAAC  
AAAAAGATGGAAGACGGGTTTCTAGATGTGTGGACATACAATGCTGAG  
CTTCTAGTTCTGATGGAAAATGAGAGGACACTTGACTTTTCATGATTCTA  
ATGTCAAGAATCTGTATGATAAAGTCAGAATGCAGCTGAGAGACAACG  
TCAAAGAACTAGGAAATGGATGTTTTGAATTTTATCACAATGTGATGA  
TGAATGCATGAATAGTGTGAAAAACGGGACGTATGATTATCCCAAGTA  
TGAAGAAGAGTCTAACTAAATAGAAATGAAATCAAAGGGGTAAAATTG  
AGCAGCATGGGGGTTTATCAAATCCTTGCCATTTATGCTACAGTAGCA  
GGTCTCTGTCACTGGCAATCATGATGGCTGGGATCTCTTTCTGGATG  
TGCTCCAACGGGTCTCTGCAGTGCAGGATCTGCATATGAGAGCTC

Fig. 35

SEQ ID NO: 43

CACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAAGAGAAG  
AGACTAATTAATTAATTAATCATCTTGAGAGAAAATGGAGAAAATAGTGCT  
TCTTCTTGCAATAGTCAGCCTTGTTAAAAGTGATCAGATTTGCATTGGTTA  
CCATGCAAACAACCTCGACAGAGCAGGTTGACACAATAATGGAAAAGAAC  
GTTACTGTTACACATGCCCAAGACATACTGGAAAAGACACACAACGGGA  
AGCTCTGCGATCTAGATGGAGTGAAGCCTCTGATTTTAAGAGATTGTAGT  
GTAGCTGGATGGCTCCTCGGAAACCCAATGTGTGACGAGTTCATCAATG  
TGCCGGAATGGTCTTACATAGTGGAGAAGGCCAACCCAGCCAATGACCT  
CTGTTACCCAGGGAATTTCAACGACTATGAAGAACTGAAACACCTATTGA  
GCAGAATAAACCATTTTGAGAAAATTGAGATCATCCCCAAAAGTTCTTGG  
TCCGATCATGAAGCCTCATCAGGGGTCAGCTCAGCATGTCCATAACCAGG  
GAACGCCCTCCTTTTTCAGAAATGTGGTATGGCTTATCAAAAAGAACAAT  
ACATACCCAACAATAAAGAGAAGCTACAATAATACCAACCAGGAAGATCT  
TTTGATACTGTGGGGGATTCATCATTCTAATGATGCGGCAGAGCAGACAA  
AGCTCTATCAAACCCAACCACCTATATTTCCGTTGGGACATCAACACTA  
AACCAGAGATTGGTACCAAAAATAGCTACTAGATCCAAAGTAAACGGGCA  
AAGTGGAAAGGATGGATTTCTTCTGGACAATTTTAAAACCGAATGATGCAA  
TCAACTTCGAGAGTAATGGAAATTTCAATTGCTCCAGAATATGCATACAAA  
ATTGTCAAGAAAGGGGACTCAGCAATTGTTAAAAGTGAAGTGGAAATATGG  
TAACTGCAATACAAAGTGTCAAACCTCAATAGGGGCGATAAACTCTAGTA  
TGCCATTCCACAACATACACCCTCTCACCATCGGGGAATGCCCAAATAT  
GTGAAATCAAACAATTAGTCCTTGCAGACTGGGCTCAGAAATAGTCCTCT  
AAGAGAAAGAAGAAGAAAAAGAGGACTATTTGGAGCTATAGCAGGGTTT  
ATAGAGGGAGGATGGCAGGGAATGGTAGATGGTTGGTATGGGTACCAC  
CATAGCAATGAGCAGGGGAGTGGGTACGCTGCAGACAAAGAATCCACTC  
AAAAGGCAATAGATGGAGTCACCAATAAGGTCAACTCGATCATTGACAAA  
ATGAACACTCAGTTTGAGGCCGTTGGAAGGGAATTTAATAACTTAGAAAG  
GAGAATAGAGAATTTAAACAAGAAAATGGAAGACGGATTCCTAGATGTCT  
GGACTTATAATGCTGAACTTCTGGTTCTCATGGAAAATGAGAGAACTCTA  
GACTTCCATGATTCAAATGTCAAGAACCTTTACGACAAGGTCCGACTACA  
GCTTAGGGATAATGCAAAGGAGCTGGGTAACGGTTGTTTCGAGTTCTAT  
CACAAATGTGATAATGAATGTATGGAAAGTGTAAAGAAACGGAACGTATGA  
CTACCCGCAGTATTCAGAAGAAGCAAGATTA AAAAGAGAGGAAATAAGT  
GGAGTAAAATTGGAATCAATAGGAACTTACCAATACTGTCAATTTATTCA  
ACAGTTGCGAGTTCTCTAGCACTGGCAATCATGGTGGCTGGTCTATCTTT  
GTGGATGTGCTCCAATGGGTCGTTACAATGCAGAATTTGCATTTAAGAGC  
TC

Fig. 36

SEQ ID NO: 44

CACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAAGAGAAGA  
GACTAATTAATTAATTAATCATCTTGAGAGAAAATGGAGAAAATAGTGCTTC  
TTTTGCAATAGTCAGTCTTGTTAAAAGTGATCAGATTTGCATTGGTTACCA  
TGCAAACAACCTCGACAGAGCAGGTTGACACAATAATGGAAAAGAACGTTA  
CTGTTACACATGCCCAAGACATACTGGAAAAGACACACAATGGGAAGCTC  
TGCGATCTAGATGGAGTGAAGCCTCTAATTTTGAGAGATTGTAGTGTAGCT  
GGATGGCTCCTCGGAAACCCAATGTGTGACGAGTTCATCAATGTGCCGGA  
ATGGTCTTACATAGTGGAGAAGGCCAATCCAGTCAATGACCTCTGTTACC  
CAGGGGATTTCAATGACTATGAAGAATTGAAACACCTATTGAGCAGAATAA  
ACCATTTTGAGAAAATTCAGATCATCCCCAAAAGTTCTTGGTCCAGTCATG  
AAGCCTCATTGGGGGTCAGCTCAGCATGTCCATACCAGGGAAAGTCCTCC  
TTTTTCAGAAATGTGGTATGGCTTATCAAAAAGAACAGTACATACCCAACA  
ATAAAGAGGAGCTACAATAATACCAACCAAGAAGATCTTTTGGTACTGTGG  
GGGATTCACCATCCTAATGATGCGGCAGAGCAGACAAAGCTCTATCAAAA  
CCCAACCACCTATATTTCCGTTGGGACATCTACACTAAACCAGAGATTGGT  
ACCAAGAATAGCTACTAGATCCAAAGTAAACGGGCAAAGTGGAAGGATGG  
AGTTCTTCTGGACAATTTTAAAACCGAATGATGCAATCAACTTCGAGAGTA  
ATGGAAATTTCAATTGCTCCAGAATATGCATACAAAATTGTCAAGAAAGGGG  
ACTCAACAATTATGAAAAGTGAATTGGAATATGGTAACTGCAATACCAAGT  
GTCAAACCTCCAATGGGGGCGATAAACTCTAGCATGCCATTCCACAATATAC  
ACCCTCTCACCATCGGGGAATGCCCAAATATGTGAAATCAAACAGATTA  
GTCCTTGCGACTGGGCTCAGAAATAGCCCTCAAAGAGAGAGAAGAAGAAA  
AAAGAGAGGATTATTTGGAGCTATAGCAGGTTTTATAGAGGGAGGATGGC  
AGGGAATGGTAGATGGTTGGTATGGGTACCACCATAGCAACGAGCAGGG  
GAGTGGGTACGCTGCAGACAAAGAATCCACTCAAAGGCAATAGATGGAG  
TCACCAATAAGGTCAACTCGATTATTGACAAAATGAACACTCAGTTTGAGG  
CCGTTGGAAGGGAATTTAACAACCTTAGAAAGGAGAATAGAGAATTTAAACA  
AGAAGATGGAAGACGGGTTCTAGATGTCTGGACTTATAATGCTGAACTT  
CTAGTTCTCATGGAAAACGAGAGAACTCTAGACTTTCATGACTCAAATGTC  
AAGAACCTTTACGACAAGGTCCGACTACAGCTTAGGGATAATGCAAAGGA  
GCTGGGTAACGGTTGTTTCGAGTTCATCATAAATGTGATAATGAATGTAT  
GGAAAGTGTAAGAAACGGAACGTATGACTACCCGCAGTATTCAGAAGAAG  
CAAGACTAAAAGAGAGGAAATAAGTGGAGTAAAATTGGAATCAATAGGA  
ATTTACCAAATATTGTCAATTTATTCTACAGTGGCCAGCTCCCTAGCACTG  
GCAATCATGGTAGCTGGTCTATCCTTATGGATGTGCTCCAATGGGTCGTT  
ACAATGCAGAATTTGCATTTAAGAGCTC

Fig. 37

SEQ ID NO: 45

CACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAAGAGAAGA  
GACTAATTAATTAATTAATCATCTTGAGAGAAAATGATTGCAATCATTGTAA  
TAGCAATACTGGCAGCAGCCGAAAGTCAGACAAGATCTGCATTGGGTAT  
CATGCCAACAAATTCAACAACACAGGTAGATACGATACTTGAGAAGAATGT  
GACTGTCACACACTCAATTGAATTGCTGGAAAATCAGAAGGAAGAAAGAT  
TCTGCAAGATATTGAACAAGGCCCTCTCGACTTAAGGGAATGTACCATA  
GAGGGTTGGATCTTGGGGAATCCCAATGCGACCTATTGCTTGGTGATCA  
AAGCTGGTCATACATTGTGGAAAGACCTACTGCTCAAACGGGATCTGCT  
ACCCAGGAACCTTAAATGAGGTAGAAGAACTGAGGGCACTTATTGGATCA  
GGAGAAAGGGTAGAGAGATTTGAGATGTTTCCCAAAGCACCTGGCAAG  
GAGTTGACACCAACAGTGAACAACAAGATCCTGCCCTTATTCTACTGGT  
GCGTCTTTCTACAGAAACCTCCTATGGATAATAAAAACCAAGACAGCAGA  
ATATCCAGTAATTAAGGGAATTTACAACAACACTGGAACCCAGCCAATCCT  
CTATTTCTGGGGTGTGCATCATCCTCCTAACACCGACGAGCAAGATACTC  
TGTATGGCTCTGGTGATCGATACGTTAGAATGGGAACTGAAAGCATGAAT  
TTTGCCAAGAGTCCGGAATTGCGGCAAGGCCTGCTGTGAATGGACAAA  
GAGGCAGAATTGATTATTATTGGTCGGTTTTAAAACCAGGGGAAACCTTG  
AATGTGGAATCTAATGGAATCTAATCGCCCCTTGGTATGCATACAAATTT  
GTCAACACAAATAGTAAAGGAGCCGTCTTCAGGTCAGATTTACCAATCGA  
GAACTGCGATGCCACATGCCAGACTATTGCAGGGTTCTAAGGACCAATA  
AAACATTTCAGAATGTGAGTCCCCTGTGGATAGGAGAATGTCCCAAATAC  
GTGAAAAGTGAAAGTCTGAGGCTTGCAACTGGACTAAGAAATGTTCCACA  
GATTGAACTAGAGGACTCTTCGGAGCTATTGCAGGGTTTATTGAAGGAG  
GATGGACTGGGATGATAGATGGGTGGTATGGCTATCACCATGAAAATTCT  
CAAGGGTCAGGATATGCAGCAGACAGAGAAAGCACTCAAAGGCTGTAA  
ACAGAATTACAAATAAGGTCAATTCCATCATCAACAAAATGAACACACAAT  
TTGAAGCTGTGCATCACGAATTTTCAAATCTGGAGAGGAGAATTGACAAT  
CTGAACAAAAGAATGCAAGATGGATTTCTGGATGTTTGGACATACAATGC  
TGAACTGTTGGTTCTTCTTGAAAACGAAAGAACAACACTAGACATGCATGACG  
CAAATGTGAAGAACCTACATGAAAAGGTCAAATCACAACCTAAGGGACAAT  
GCTACGATCTTAGGGAATGGTTGCTTTGAATTTTGGCATAAGTGTGACAAT  
GAATGCATAGAGTCTGTCAAAAATGGTACATATGACTATCCCAAATACCAG  
ACTGAAAGCAAATTAACAGGCTAAAATAGAATCAGTAAAGCTAGAGAAC  
CTTGGTGTGTATCAAATTTGCCATTTATAGTACGGTATCGAGCAGCCTA  
GTGTTGGTAGGGCTGATCATGGCAATGGGTCTTTGGATGTGTTCAAATGG  
TTCAATGCAGTGCAGGATATGTATATAAGAGCTC

Fig. 38

SEQ ID NO: 46

CACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAAGAGAAGA  
GACTAATTAATTAATTAATCATCTTGAGAGAAAATGAACTCAAATTCTAA  
TATTAGCCACTTCGGCATTCTTCTATGTACGTGCAGATAAAATCTGCCTAG  
GACATCATGCTGTGTCTAATGGAACCAAAGTAGACACCCTTACTGAAAA  
GGAATAGAAGTTGTCAATGCAACAGAAACAGTTGAACAAACAAACATCCC  
TAAGATCTGCTCAAAGGAAAACAGACTGTTGACCTTGGTCAATGTGGAT  
TACTAGGGACCGTTATTGGTCCTCCCAATGTGACCAATTTCTTGAGTTCT  
CTGCTAATTTAATAGTTGAAAGAAGGGAAGGTAATGACATTTGTTATCCAG  
GCAAATTTGACAATGAAGAAACATTGAGAAAAATACTCAGAAAATCCGGA  
GGAATTA AAAAGGAGAATATGGGATTCACATATACCGGAGTGAGAACCAA  
TGGAGAGACTAGCGCATGTAGAAGGTCAAGATCTTCCTTTTATGCAGAGA  
TGAAATGGCTTCTATCCAGCACAGACAATGGGACATTTCCACAAATGACA  
AAGTCCTACAAGAACACTAAGAAGGTACCAGCTCTGATAATCTGGGGAAT  
CCACCCTCAGGATCAACTACTGAACAGACTAGATTATATGGAAGTGGGA  
ATAAATTGATAACAGTTTGGAGTTCCAAATACCAACAATCTTTTGTCCCAA  
ATCCTGGACCAAGACCGCAAATGAATGGTCAATCAGGAAGAATTGACTTT  
CACTGGCTGATGCTAGATCCCAATGATACTGTCACTTTTCAAGTTTTAATGGG  
GCCTTTATAGCACCTGACCGCGCCAGTTTTCTAAGAGGTAAATCTCTAGG  
AATCCAAAGTGATGCACAACCTTGACAATAATTGTGAAGGTGAATGCTATCA  
TATTGGAGGTACTATAATTAGCAACTTGCCCTTTCAAACATTAATAGTAG  
GGCAATCGGAAAATGCCCCAGATACGTGAAGCAGAAGAGCTTAATGCTA  
GCAACAGGAATGAAAAATGTTCCCTGAAGCTCCTGCACATAAAACAAC  
TCATCACATGCGCAAAAAAAGAGGTTTATTTGGTGCAATAGCAGGATTCAT  
TGAAAATGGGTGGGAAGGATTAATAGACGGATGGTATGGATATAAGCATC  
AGAATGCACAAGGAGAAGGGACTGCTGCAGACTACAAAAGTACACAATCT  
GCTATCAACCAATAAACCGGAAAATTGAACAGACTAATAGAAAAACCAAC  
CAGCAATTCGAACATAATAGATAATGAGTTCAATGAAATAGAAAAACAAAT  
GGCAATGTTATTA ACTGGACTAGAGATTCTATCATCGAAGTATGGTCATAT  
AATGCAGAGTTCCTCGTAGCAGTGGAGAATCAACACACTATTGATTTAACT  
GACTCAGAAATGAACAACTATATGAAAAGGTAAGAAGACAACACTGAGAGA  
AAATGCTGAGGAAGATGGTAATGGCTGTTTTGAAATATTCCACCAATGTG  
ACAATGATTGCATGGCCAGCATTAGAAACAACACATATGACCATAAAAAAT  
ACAGAAAAGAGGCAATACAAAACAGAATCCAGATTGACGCAGTAAAGTTG  
AGCAGTGGTTACAAAGATATAACTTTGGTTTAGCTTCGGGGCATCATG  
TTTCTTATTTCTTGCCATTGCAATGGGTCTTGTTTTCATATGTATAAAAAAT  
GGAAACATGCGGTGCACTATTTGTATATAAGAGCTC

Fig. 39

SEQ ID NO: 47

CACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAAGAGAAGA  
GACTAATTAATTAATTAATCATCTTGAGAGAAAATGGAAACAATATCACTAA  
TAACTATACTACTAGTAGTAACAGCAAGCAATGCAGATAAAATCTGCATCG  
GCCACCAGTCAACAACTCCACAGAACTGTGGACACGCTAACAGAAACC  
AATGTTCTGTGACACATGCCAAAGAATTGCTCCACACAGAGCATAATGGA  
ATGCTGTGTGCAACAAGCCTGGGACATCCCCTCATTCTAGACACATGCAC  
TATTGAAGGACTAGTCTATGGCAACCCTTCTTGACCTGCTGTTGGGAG  
GAAGAGAATGGTCCTACATCGTCGAAAGATCATCAGCTGTAATGGAACG  
TGTTACCCTGGGAATGTAGAAAACCTAGAGGAACTCAGGACACTTTTTAGT  
TCCGCTAGTTCCTACCAAAGAATCCAAATCTTCCCAGACACAACCTGGAAT  
GTGACTTACACTGGAACAAGCAGAGCATGTTCAAGTTTCAATTCTACAGGAG  
TATGAGATGGCTGACTCAAAGAGCGGTTTTTACCCTGTTCAAGACGCC  
AATACACAAATAACAGGGGAAAGAGCATTCTTTTCGTGTGGGCATACAT  
CACCCACCCACCTATACCGAGCAAACAAATTTGTACATAAGAAACGACACA  
ACAACAAGCGTGACAACAGAAGATTTGAATAGGACCTTCAAACCAGTGATA  
GGGCCAAGGCCCTTGTCATGGTCTGCAGGGAAGAATTGATTATTATTG  
GTCGGTACTAAACCAGGCCAAACATTGCGAGTACGATCCAATGGGAATC  
TAATTGCTCCATGGTATGGACACGTTCTTTTCAGGAGGGAGCCATGGAAGA  
ATCCTGAAGACTGATTTAAAAGGTGGTAATTGTGTAGTGCAATGTCAGACT  
GAAAAGGTGGCTTAAACAGTACATTGCCATTCCACAATATCAGTAAATAT  
GCATTTGGAACCTGCCCAAATATGTAAGAGTTAATAGTCTCAAACCTGGCA  
GTCGGTCTGAGGAACGTGCCTGCTAGATCAAGTAGAGGACTATTTGGAGC  
CATAGCTGGATTCATAGAAGGAGGTTGGCCAGGACTAGTCGCTGGCTGG  
TATGGTTTCCAGCATTCAAATGATCAAGGGGTTGGTATGGCTGCAGATAG  
GGATTCAACTCAAAGGCAATTGATAAAATAACATCCAAGGTGAATAATAT  
AGTCGACAAGATGAACAAGCAATATGAAATAATTGATCATGAATTTAGTGA  
GGTTGAACTAGACTCAATATGATCAATAATAAGATTGATGACCAAATACA  
AGACGTATGGGCATATAATGCAGAATTGCTAGTACTACTTGAAAATCAAAA  
AACACTCGATGAGCATGATGCGAACGTGAACAATCTATATAACAAGGTGA  
AGAGGGCACTGGGCTCCAATGCTATGGAAGATGGGAAAGGCTGTTTCGA  
GCTATACCATAAATGTGATGATCAGTGCATGGAAACAATTCCGAACGGGA  
CCTATAATAGGAGAAAGTATAGAGAGGAATCAAGACTAGAAAGGCAGAAA  
ATAGAGGGGGTTAAGCTGGAATCTGAGGGAACCTTACAAAATCCTCACCAT  
TTATTGACTGTCGCCTCATCTCTTGCTTGCAATGGGGTTTGCTGCCTT  
CCTGTTCTGGGCCATGTCCAATGGATCTTGCAAGATGCAACATTTGTATATA  
AGAGCTC

**Fig. 40A**

SEQ ID NO: 48

MKVKLLVLLCTFTATYADTICIGYHANNSTDTVDTVLEKNVTVTHSVNLLNSH  
NGKLCLLKGIAPLQLGNCSVAGWILGNPECELLISKESWSYIVEKPNPENGTCY  
PGHFADYEELREQLSSVSSFERFEIFPKESSWPNHVTGVSASC SHNGESSF  
YRNLLWLTGKNGLYPNLSKSYANNKEKEVLVLWGVHHPNIGDQKALYHTEN  
AYVSVSSHYSRKFTPEIAKRPKVRDQEGRINYYWTLLEPGDTIIFEANGNLIAP  
RYAFALSRGFGSGIINSNAPMDKCDACQTPQGAINSSLPFQNVHPVTIGCEP  
KYVRSACL RMVTGLRNIPSIQSRGLFGAIAGFIEGGWTGMVDGWYGYHHQNE  
QGSGYAADQKSTQNAINGITNKVNSVIEKMNTQFTAVGKEFNKLERRMENLNK  
KVDDGFIDIWTYNAELLVLLNERTLDFHDSNVKNLYEKVKSQKNNAKEIGNG  
CFEFYHKCNDECMESVKNGTYPKYSEESKLNREKIDGVKLESMGVYQILAI  
YSTVASSLVLLVSLGAISFWMCSNGSLQCRICI

**Fig. 40B**

SEQ ID NO: 49

MKVKLLVLLCTFTATYADTICIGYHANNSTDTVDTVLEKNVTVTHSVNLLNSH  
NGKLCLLKGIAPLQLGNCSVAGWILGNPECELLISRESWSYIVEKPNPENGTCY  
PGHFADYEELREQLSSVSSFERFEIFPKESSWPNH TTTGVSASC SHNGESSFY  
KNLLWLTGKNGLYPNLSKSYANNKEKEVLVLWGVHHPNIGDQRALYHKENA  
YVSVSSHYSRKFTPEIAKRPKVRDQEGRINYYWTLLEPGDTIIFEANGNLIAPR  
YAFALSRGFGSGIINSNAPMDECDACQTPQGAINSSLPFQNVHPVTIGCEPK  
YVRSACL RMVTGLRNIPSIQSRGLFGAIAGFIEGGWTGMVDGWYGYHHQNEQ  
GSGYAADQKSTQNAINGITNKVNSVIEKMNTQFTAVGKEFNKLERRMENLNKK  
VDDGFIDIWTYNAELLVLLNERTLDFHDSNVKNLYEKVKSQKNNAKEIGNGC  
FEFYHKCNDECMESVKNGTYPKYSEESKLNREKIDGVKLESMGVYQILAIY  
STVASSLVLLVSLGAISFWMCSNGSLQCRICI

**Fig. 41A**

SEQ ID NO: 50

MKTIIALSYILCLVFTQKLPGNDNSTATLCLGHHAVPNGTIVKTITNDQIEVTN  
ATELVQSSSTGEICDSPHQILDGENCTLIDALLGDPQCDGFQNKKWDLFVE  
RSKAYSNCYPYDVPDYASLRSLVASSGTLEFNNEFSNWTGVTQNGTSSA  
CIRRSNNSFFSRLNWLTHLKFKYPALNVTMPNNEKFDKLYIWGVHHPGTD  
NDQIFLYAQASGRITVSTKRSQQTVIPNIGSRPRVRNIPSRISIWWTIVKPGDI  
LLINSTGNLIAPRGYFKIRSGKSSIMRSDAPIGKCNSECITPNGSIPNDKPFQ  
NVNRITYGACPRYVKQNTLKLATGMRNVPEKQTRGIFGAIAGFIENGWEG  
MVDGWYGFRRHQNSEGIGQAADLKSTQAADQINGKLNRLIGKTNEKFHQIE  
KEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTSEMKNLFF  
EKTKKQLRENAEDMGNGCFKIYHKCDNACIGSIRNGTYDHDVYRDEALNN  
RFQIKGVELKSGYKDWILWISFAISCFLLCVALLGFIMWACQKGNIRCNICI

**Fig. 41B**

SEQ ID NO: 51

MKTIIALSYILCLVFTQKLPGNDNSTATLCLGHHAVPNGTIVKTITNDQIEVTN  
ATELVQSSSTGGICDSPHQILDGENCTLIDALLGDPQCDGFQNKKWDLFVE  
RSKAYSNCYPYDVPDYASLRSLVASSGTLEFNDESFNWTGVTQNGTSSA  
CKRRSNNSFFSRLNWLTHLKFKYPALNVTMPNNEKFDKLYIWGVHHPGTD  
NDQIFLHAQASGRITVSTKRSQQTVIPNIGSRPRIRNIPSRISIWWTIVKPGDI  
LLINSTGNLIAPRGYFKIRSGKSSIMRSDAPIGKCNSECITPNGSIPNDKPFQ  
NVNRITYGACPRYVKQNTLKLATGMRNVPEKQTRGIFGAIAGFIENGWEG  
MVDGWYGFRRHQNSEGIGQAADLKSTQAAINQINGKLNRLIGKTNEKFHQIE  
KEFSEVEGRIQDLEKYVEDTKIDLWSYNAELLVALENQHTIDLTSEMKNLFF  
ERTKKQLRENAEDMGNGCFKIYHKCDNACIGSIRNGTYDHDVYRDEALNN  
RFQIKGVELKSGYKDWILWISFAISCFLLCVALLGFIMWACQKGNIRCNICI

**Fig. 42A**

SEQ ID NO: 52

MKAIIVLLMVVTSNADRICTGITSSNSPHVVKATQGEVNVTVIPLTTTPTKS  
HFANLKGTETRGKLCPKCLNCTDLVALGRPKCTGNIPSARVSILHEVRPVT  
SGCFPIMHDRTKIRQLPKLLRGYEHRLSTHNVINAENAPGGPYKIGTSGSCP  
NVTNGNGFFATMAWAVPKNDNNKTATNSLTIEVPYICTEGEDQITVWGFHS  
DNETQMAKLYGDSKPQKFTSSANGVTTHYVSQIGGFNPQTEDGGLPQSGRI  
VVDYMVQKSGKTGTITYQRGILLPQKWCASGRSKVIKGSPLIGEADCLHE  
KYGGLNKSKPYTGEHAKAIGNCPIWVKTPLKLANGTKYRPPAKLLKERGFF  
GAIAGFLEGGWEGMIAGWHGYTSHGAHGVAVAADLKSTQEAINKITKNLNS  
LSELEVKNLQRLSGAMDELHNEILELDEKVDDLADTSSQIELAVLLSNEGII  
SEDEHLLALERKLLKMLGPSAVEIGNGCFETKHKCNQTCLDRIAAGTFDAGE  
FSLPTFDSLNTAASLNDGDLNHTILLYSTAASSLAVTLMIAIFVVMVSRD  
NVSCSICL

**Fig. 42B**

SEQ ID NO: 53

MKAIIVLLMVVTSNADRICTGITSSNSPHVVKATQGEVNVTVIPLTTTPTKS  
YFANLKGTRTRGKLCPDCLNCTDLVALGRPMCVGTTPSAKASILHEVKPVT  
SGCFPIMHDRTKIRQLPNLLRGYENIRLSTQNVIDAEKAPGGPYRLGTSGSC  
PNATSKSGFFATMAWAVPKDNNKNATNPLTVEVPYICTEGEDQITVWGFHS  
DNKTQMKNLYGDSNPQKFTSSANGVTTHYVSQIGSFPDQTEDGGLPQSGRI  
VVDYMMQKPGKTGTIVYQRGVLLPQKWCASGRSKVIKGSPLIGEADCLH  
EKYGGLNKSKPYTGEHAKAIGNCPIWVKTPLKLANGTKYRPPAKLLKERGF  
FGAIAGFLEGGWEGMIAGWHGYTSHGAHGVAVAADLKSTQEAINKITKNLN  
SLSELEVKNLQRLSGAMDELHNEILELDEKVDDLADTSSQIELAVLLSNEGII  
NSEDEHLLALERKLLKMLGPSAVEIGNGCFETKHKCNQTCLDRIAAGTFNAG  
EFSLPTFDSLNTAASLNDGDLNHTILLYSTAASSLAVTLMIAIFIVVMVSRD  
NVSCSICL

**Fig. 43A**

SEQ ID NO: 54

MAIYLILLFTAVRGDQICIGYHANNSTEKVDTILERNVTVTHAKDILEKTHNGKLC  
KLNIGIPPLELGDCSIAGWLLGNPECDRLLSVPEWSYIMEKENPRDGLCYPGSF  
NDYEELKHLLSSVKHFEKVILPKDRWTQHNTTGGSRACAVSGNPSFFRNMV  
WLTKKESNYPVAKGSYNNTSGEQMLIIVGVHHPNDETEQRTLYQNVGTYVSV  
GTSTLNKRSTPDIATRPKVNGLGSRMEFSWTLLDMWDTINFESTGNLIAPEYGF  
KISKRGSSGIMKTEGTLENCETKCQTPLGAINTTLPFHNHPLTIGECPKYVKSE  
KLVLATGLRNVPQIESRGLFGAIAAGFIEGGWQGMVDGWYGYHHSNDQGSFYA  
ADKESTQKAFDGITNKVNSVIEKMNTQFEAVGKEFSNLERRLENLNKKMEDGFL  
DVWTYNAELLVLMENERTLDFHDSNVKNLYDKVRMQLRDNVKELGNGCFEFY  
HKCDDECMNSVKNGTYPKYEEESKLNREIKGVKLSSMGVYQILAIYATVAG  
SLSLAIMMAGISFWMCSNGSLQCRICI

**Fig. 43B**

SEQ ID NO: 55

MEKIVLLLAIVSLVKSDQICIGYHANNSTEQVDTIMEKNVTVTHAQDILEKTHNGK  
LCDLDGVKPLILRDCSVAGWLLGNPMCDEFINVPWSYIVEKANPANDLCYPG  
NFNDYEELKHLLSRINHFEEKIIPKSSWSDHEASSGVSSACPYQGTPSFFRNVV  
WLIKKNNTYPTIKRSYNNTNQEDLLILWGIHHSNDAAEQTKLYQNPTTYISVGTS  
TLNQRLVPKIATRSKVNQSGRMDFFWTILKPNDAINFESNGNFIAPEYAYKIVK  
KGDSIVKSEVEYGNCNTKCQTPIGAINSSMPFHNIHPLTIGECPKYVKSNNKLV  
ATGLRNSPLRERRRRKRGLFGAIAAGFIEGGWQGMVDGWYGYHHSNEQGSFYA  
ADKESTQKAIDGVTNKVNSIIDKMNTQFEAVGREFNNLERRRIENLNKKMEDGFL  
DVWTYNAELLVLMENERTLDFHDSNVKNLYDKVRLQLRDNVAKELGNGCFEFYH  
KCDNECMESVRNGTYDYPQYSEEARLKRREEISGVKLESIGTYQILSIYSTVASSL  
ALAIMVAGLSLWMCSNGSLQCRICI

**Fig. 44A**

SEQ ID NO: 56

MEKIVLLFAIVSLVKSDQICIGYHANNSTEQVDTIMEKNVTVTHAQDILEKTHNGKL  
CDLDGVKPLILRDCSVAGWLLGNPMCDEFINPEWSYIVEKANPVNDLCYPGDF  
NDYEELKHLISRINHFEDIQIIPKSSWSSHEASLGVSSACPYQGKSSFFRNWWLI  
KKNSTYPTIKRSYNNTNQEDLLVLWGIHHPNDAAEQTKLYQNPTTYISVGTSTLN  
QRLVPRIATRSKVNQSGRMEFFWTILKPNDAINFESNGNFIAPYAYKIVKKGD  
STIMKSELEYGNCNTKCQTPMGAINSSMPFHNIHPLTIGECPKYVKSRLVLTG  
LRNSPQRERRRKKRGLFGAIAGFIEGGWQGMVDGWYGYHHSNEQGSYAAD  
KESTQKAIDGVTNKVNSIIDKMNTQFEAVGREFNNLERRIENLNKKMEDGFLDV  
WTYNAELLVLMENERTLDFHDSNVKNLYDKVRLQLRDNKELGNGCFEFYHKC  
DNECMESVRNGTYDYPQYSEEARLKREEISGVKLESIGIYQILSIYSTVASSLALAI  
MVAGLSLWMCSNGSLQCRICI

**Fig. 44B**

SEQ ID NO: 57

MIAIIVAILAAAGKSDKICIGYHANNSTTQVDTILEKNVTVTHSIELLENQKEERFCK  
ILNKAPLDLRECTIEGWILGNPQC DLLLGDQSWSYIVERPTAQNGICYPGTLNEV  
EELRALIGSGERVERFEMFPQSTWQGVDTNSGTTRSCPYSTGASFYRNLLWIK  
TKTAEYPVIKGIYNNTGTQPILYFWGVHHPNTDEQDTLYGSGDRYVRMGTESM  
NFAKSPEIAARPAVNGQRGRIDYYWSVLKPGETLNVESNGNLIAPWYAYKFVNT  
NSKGAVFRSDLPIENC DATCQTIAGVLRNKT FQNV SPLWIGECPKYVKSESLRL  
ATGLRNVPQIETRGLFGAIAGFIEGGWTGMIDGWYGYHHENSQGSYAADRES  
TQKAVNRITNKVNSIINKMNTQFEAVDHEFSNLERRIDNLNKRMQDGFLDWWTY  
NAELLVLENER TLDMDANVKNLHEKVKSQLRDNATILGNGCFEFWHKCDNEC  
IESVKNGTYDYPKYQTESKLNRLKIESVKLENLGVYQILAIYSTVSSSLVLVGLIMA  
MGLWMCSNGSMQCRICI

**Fig. 45A**

SEQ ID NO: 58

MNTQILILATS AFFYVRADKICLGHHAVSNGTKVDTLTEKGIEVVNATETVEQT  
NIPKICSKGKQTVDLGQCGLLGTVIGPPQCDQFLEFSANLIVERREGNDICYPG  
KFDNEETLRKILRKSGGIKKENMGFTYTGVRTNGETSACRRSRSSFYAEMKW  
LLSSTDNGTFPQMTKSYKNTKKVPALIIWGIHHSGSTTEQTRLYGSGNKLITV  
WSSKYQQSFVPNPGPRPQMNGQSGRIDFHWLMLDPNDTVTF SFNGAFIAPD  
RASFLRGKSLGIQSDAQLDNNCEGECYHIGGTIISNLPFQNINSRAIGKCPRYV  
KQKSLMLATGMKNVPEAPAHKQLTHHMRKKRGLFGAIAGFIENGWEGLIDG  
WYGYKHQNAQGEGTAADYKSTQSAINQITGKLNRLIEKTNQQFELIDNEFNEI  
EKQIGNVINWTRDSIIEVWSYNAEFLVAVENQHTIDLTDSEMKNLYEKVRRQL  
RENAEEDGNGCFEIFHQCDNDCMASIRNNTYDHKKYRKEAIQNR IQIDAVKLS  
SGYKDIIWF SFGASCFLFLAIAMGLVFICIKNGNMRCTICI

**Fig. 45B**

SEQ ID NO: 59

METISLITILLVVTASNADKICIGHQSTNSTETVDTLTETNVPVTHAKELLHTEHN  
GMLCATSLGHPLILDCTIEGLVYGNPSCDLLLGGREWSYIVERSSAVNGTCY  
PGNVENLEELRTL FSSASSYQRIQIFPD TTWNVTYTGTSRACSGSFYRSMRW  
LTQKSGFY PVQDAQYTNNRGKSILFVWGIHHPPTYTEQTNLYIRNDTTTSVTT  
EDLNRTFKPVIGPRPLVNLQGRIDYYWSVLKPGQTLRVR SNGNLIAPWYGH  
VLSGGSHGRILKTDLKG GNCVVQCQTEKGGLNSTLPFHNISKYAFGTCPKYV  
RVNSLKLAVGLRNVPARSSRGLFGAIAGFIEGGWPGLVAGWYGFQHSNDQG  
VGMAADR DSTQKAIDKITSKVNNIVDKM NKQYEIIDHEFSEVETRLNMINNKID  
DQIQDVWAYNAELLV LLENQKTLDEHDANVNNLYNKVKRALG S NAMEDGKG  
CFELYHKCDDQCMETIRNGTYNRRKYREESRLERQKIEGVKLESEGTYKILTI  
YSTVASSLV LAMGFAAFLFWAMSN GSCRCNICI

Fig. 46

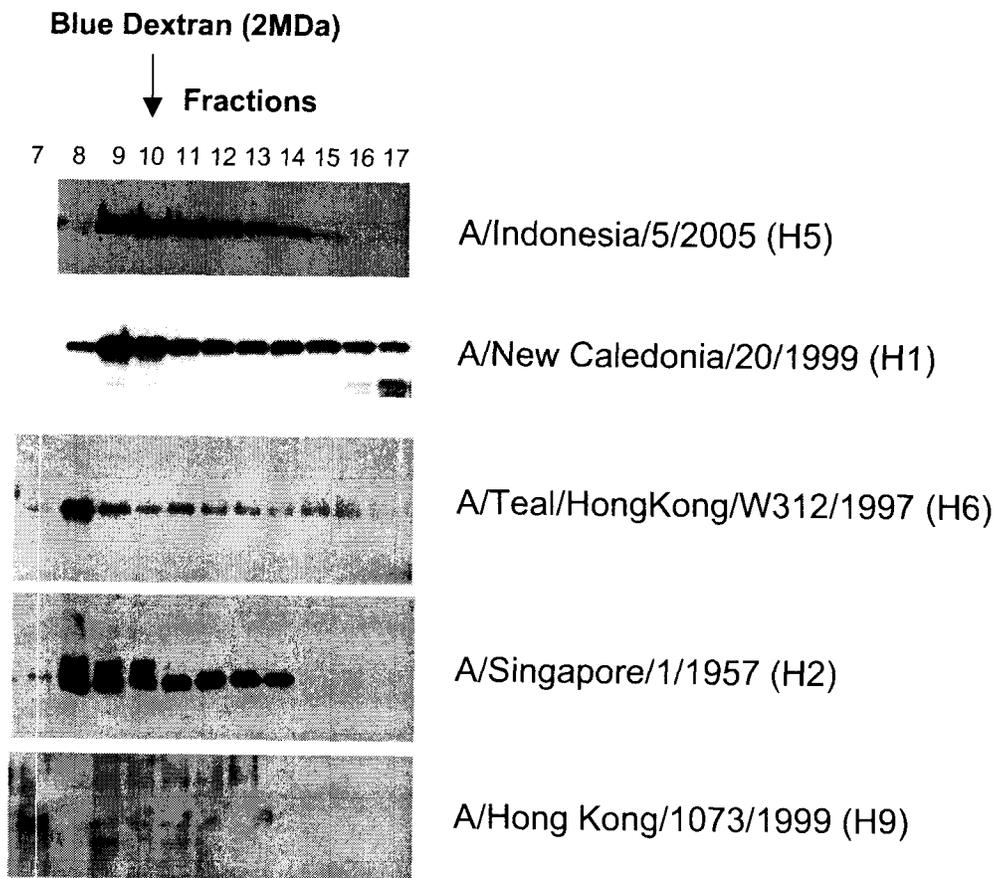


Fig. 47

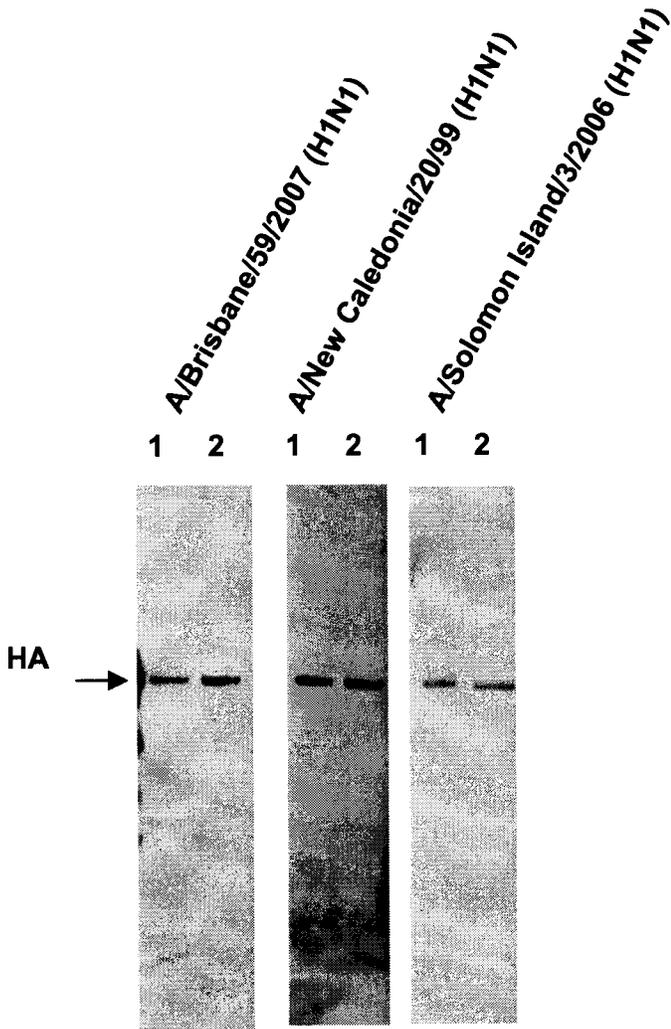


Fig. 48

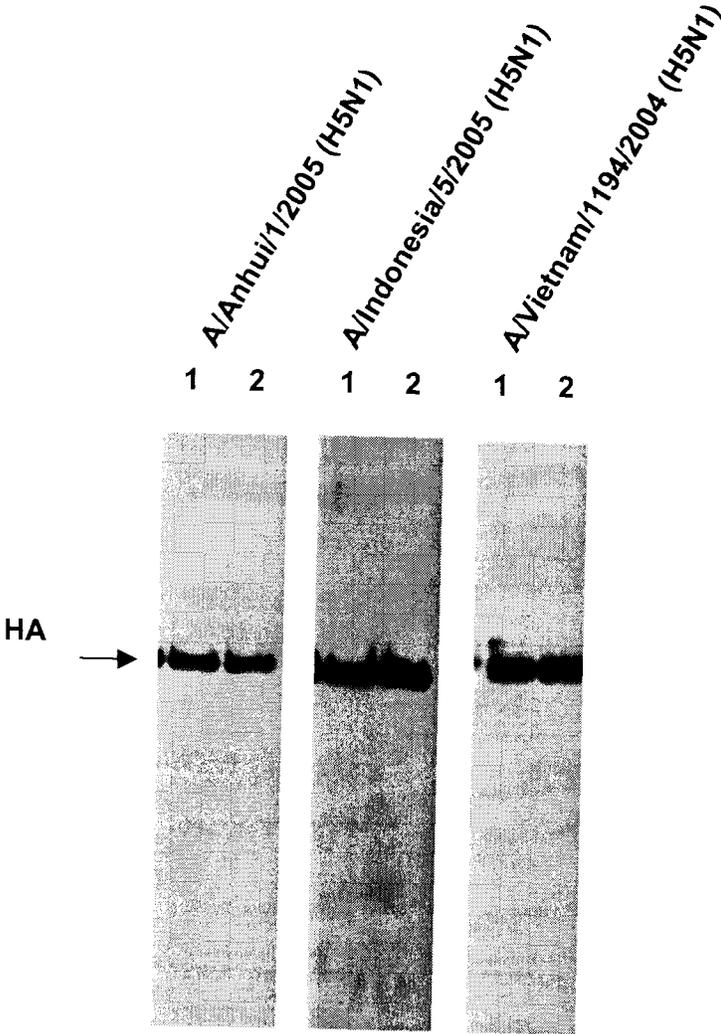


Fig. 49

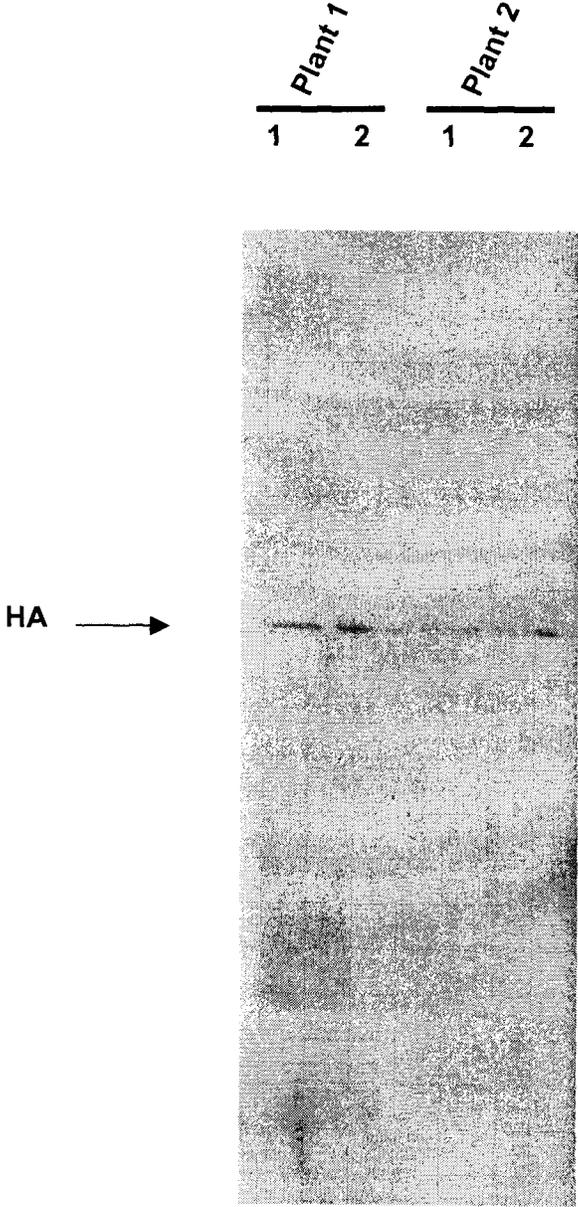


Fig. 50A

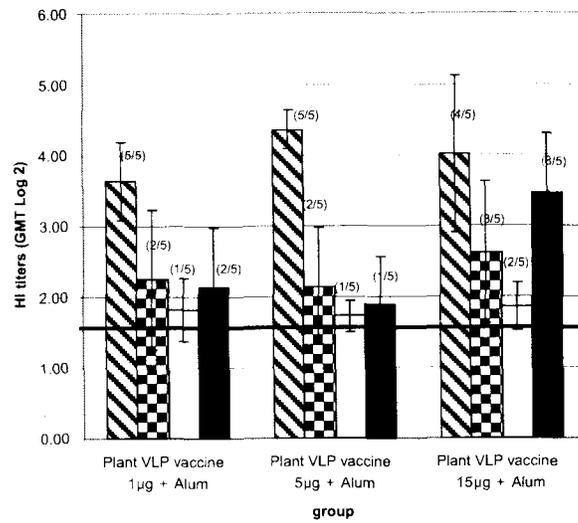


Fig. 50B

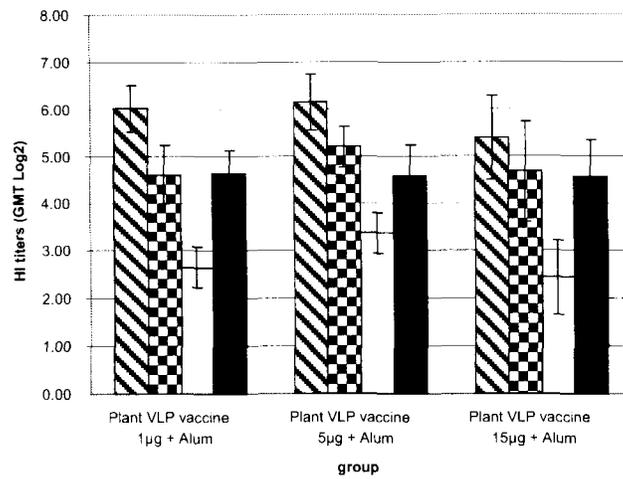


Fig. 51

SEQ ID NO: 60

H5 from A/Indonesia/5/2005 (Construct # 660)

AGAGGTACCCCGGGCTGGTATATTTATATGTTGTCAAATAACTCAAAAACCATAAAAAGTTTAAAGTT  
AGCAAGTGTGTACATTTTTACTTGAACAAAAATATTACCTACTACTGTTATAAATCATTATTAAC  
ATTAGAGTAAAGAAATATGGATGATAAGAACAAGAGTAGTGATATTTTGACAACAATTTTGTTGCA  
ACATTTGAGAAAATTTTGTGTTCTCTCTTTTCATTGGTCAAAAAACAATAGAGAGAGAAAAAGGAA  
GAGGGAGAATAAAAACATAATGTGAGTATGAGAGAGAAAGTTGTACAAAAGTTGTACAAAATAG  
TTGTACAAATATCATTGAGGAATTTGACAAAAGCTACACAAATAAGGGTTAATTGCTGTAATAAAA  
TAAGGATGACGCATTAGAGAGATGTACCATTAGAGAATTTTTGGCAAGTCATTA AAAAGAAAGAAT  
AAATTATTTTTAAAATTTAAAAGTTGAGTCATTTGATTAACATGTGATTATTTAATGAATTGATGAAA  
GAGTTGGATTAAGTTGTATTAGTAATTAGAATTTGGTGTCAAATTTAATTTGACATTTGATCTTTT  
CCTATATATTGCCCATAGAGTCAGTTAACTCATTTTTATATTTTCATAGATCAAATAAGAGAAATAA  
CGGTATATTAATCCCTCCAAAAA AAAAAACGGTATATTTACTAAAAATCTAAGCCACGTAGGAG  
GATAACAGGATCCCGTAGGAGGATAACATCCAATCCAACCAATCACAACAATCCTGATGAGATA  
ACCCACTTTAAGCCACGCATCTGTGGCACATCTACATTATCTAAATCACACATTTCCACACAT  
CTGAGCCACACAAAAACCAATCCACATCTTTATCACCCATTCTATAAAAAATCACACTTTGTGAGT  
CTACACTTTGATTCCCTTCAAACACATACAAAGAGAAGAGACTAATTAATTAATTAATCATCTTGA  
GAGAAAATGGAGAAAATAGTGCTTCTTCTTGAATAGTCAGTCTTGTTAAAAGTGATCAGATTTGC  
ATTGGTTACCATGCAACAATTAACAGAGCAGGTTGACACAATCATGGAAAAGAACGTTACTGT  
TACACATGCCAAGACATACTGGAAAAGACACACAACGGGAAGCTCTGCGATCTAGATGGAGTG  
AAGCCTCTAATTTAAGAGATTGTAGTGTAGCTGGATGGCTCCTCGGAACCAATGTGTGACGA  
ATTCATCAATGTACCGGAATGGTCTTACATAGTGGAGAAGGCCAATCCAACCAATGACCTCTGTT  
ACCCAGGGAGTTTCAACGACTATGAAGAACTGAAACACCTATTGAGCAGAATAAACCATTTTGAG  
AAAATTCAAATCATCCCCAAAAGTCTTGGTCCGATCATGAAGCCTCATCAGGAGTTAGCTCAGC  
ATGTCCATACCTGGGAAGTCCCTCCTTTTTAGAAATGTGGTATGGCTTATCAAAAAGAACAGTA  
CATACCCAACAATAAAGAAAAGCTACAATAATACCAACCAAGAGGATCTTTTGGTACTGTGGGGA  
ATTCACCATCCTAATGATGCGGCAGAGCAGACAAGGCTATATCAAACCCAACCACTATATTTCC  
CATTGGGACATCAACACTAAACCAGAGATTGGTACCAAAAATAGCTACTAGATCCAAAGTAAACG  
GGCAAAGTGAAGGATGGAGTTCTTCTGGACAATTTTAAAACCTAATGATGCAATCAACTTCGAG  
AGTAATGGAATTTTCATTGCTCCAGAATATGCATACAAAATTGTCAAGAAAGGGGACTCAGCAATT  
ATGAAAAGTGAATTGGAATATGGTAACTGCAACACCAAGTGTCAAACCTCAATGGGGGCGATAAA  
CTCTAGTATGCCATTCACAACATACACCCTCTACCATCGGGGAATGCCCAAATATGTGAAAT  
CAAACAGATTAGTCCTTGAACAGGGCTCAGAAATAGCCCTCAAAGAGAGAGCAGAAGAAAAA  
GAGAGGACTATTTGGAGCTATAGCAGTTTTATAGAGGGAGGATGGCAGGGAATGGTAGATGGT  
TGGTATGGGTACCACCATAGCAATGAGCAGGGGAGTGGGTACGCTGCAGACAAAGAATCCACTC  
AAAAGGCAATAGATGGAGTCACCAATAAGGTCAACTCAATCATTGACAAAATGAACACTCAGTTT  
GAGGCCGTTGGAAGGGAATTTAATAACTTAGAAAGGAGAATAGAGAATTTAAACAAGAAGATGGA  
AGACGGGTTTCTAGATGTCTGGACTTATAATGCCGAACCTTCTGGTTCTCATGAAAAATGAGAGAA  
CTCTAGACTTTTCATGACTCAAATGTTAAGAACCTCTACGACAAGGTCGACTACAGCTTAGGGAT  
AATGCAAAGGAGCTGGGTAACGGTTGTTTCGAGTTCTATCAAAATGTGATAATGAATGTATGGA  
AAGTATAAGAAACGGAACGTACAACATCCGCAGTATTCCAGAAGAAGCAAGATTA AAAAGAGAGG  
AAATAAGTGGGGTAAAATTTGGAATCAATAGGAACCTTACCAAATCTGTCAATTTATTCAACAGTGG  
CGAGTTCCCTAGCACTGGCAATCATGATGGCTGGTCTATCTTTATGGATGTGCTCCAATGGATCG  
TTACAATGCAGAAATTTGCATTTAAGAGCTCTAAGTTAAAATGCTTCTTCGCTCTCTATTTATAAT  
GGTTTGTTATTGTTAATTTGTTCTTGTAGAAGAGCTTAATTAATCGTTGTTGTTATGAAATACTAT  
TTGTATGAGATGAACTGGTGAATGTAATTCATTACATAAGTGGAGTCAGAATCAGAATGTTTCC  
TCCATAACTAAGTACATGAAGACCTGCCGCTACAATTGCTTATATTTGAACAACATAAATTTG  
AACACTTTTTGCCACAACCTTTATAAGTGGTTAATATAGCTCAAATATATGGTCAAGTTCAATAGATT  
AATAATGGAATATCAGTTATCGAAATTCATTAACAATCAACTTAACGTTATTAACTACTAATTTTAT  
ATCATCCCTTTGATAAATGATAGTACA

Fig. 52

SEQ ID NO: 61

**H1 from A/New Caledonia/20/1999 (Construct # 540)**

AGAGGTACCCCGGGCTGGTATATTTATATGTTGTCAAATAACTCAAAAACCATAAAAAGTTAAGTT  
AGCAAGTGTGTACATTTTTACTTGAACAAAAATATTCACCTACTACTGTTATAAATCATTATTAAC  
ATTAGAGTAAAGAAATATGGATGATAAGAACAAGAGTAGTGATTTTTGACAACAATTTTTGTTGCA  
ACATTTGAGAAAATTTGTTGTTCTCTCTTTTCATTGGTCAAAAACAATAGAGAGAGAAAAAGGAA  
GAGGGAGAATAAAAACATAATGTGAGTATGAGAGAGAAAGTTGTACAAAAGTTGTACCAAATAG  
TTGTACAAATATCATTGAGGAATTTGACAAAAGCTACACAAATAAGGGTTAATTGCTGTAAATAAA  
TAAGGATGACGCATTAGAGAGATGTACCATTAGAGAATTTTTGGCAAGTCATTAAGAAAGAAAGAA  
TAAATTATTTTTAAAATTAAGTTGAGTCATTTGATTAACATGTGATTATTTAATGAATTGATGAA  
AGAGTTGGATTAAAGTTGATTAGTAATTAGAATTTGGTGTCAAATTTAATTTGACATTTGATCTTT  
TCCTATATATTGCCCATAGAGTCAGTAACTCATTTTTATATTTTCATAGATCAAATAAGAGAAATA  
ACGGTATATTAATCCCTCCAAAAAACAACGGTATATTTACTAAAAAATCTAAGCCACGTAGGA  
GGATAACAGGATCCCCGTAGGAGGATAACATCCAATCCAACCAATCACAACAATCCCTGATGAGA  
TAACCCACTTTAAGCCACGCATCTGTGGCACATCTACATTATCTAAATCACACATTTCTCCACAC  
ATCTGAGCCACACAAAAACCAATCCACATCTTTATCACCCATTCTATAAAAAATCACACTTTGTGA  
GTCTACACTTTGATCCCTTCAAACACATACAAAGAGAAGAGACTAATTAATTAATTAATCATCTT  
GAGAGAAAATGGCGAAAAACGTTGCGATTTTCGGCTTATTGTTTTCTCTTCTTGTGTTGGTTCTT  
CTCAGATCTTCGCTGACACAATATGTATAGGCTACCATGCCAACAACTCAACCGACACTGTTGAC  
ACAGTACTTGAGAAGAATGTGACAGTGACACACTCTGTCAACCTACTTGAGGACAGTACAATG  
GAAAACATGTCTACTAAAAGGAATAGCCCCACTACAATTTGGTAATTGCAGCGTTGCCGGATG  
GATCTTAGGAAACCCAGAATGCGAATTAATGATTTCCAAGGAATCATGGTCTACATTGTAGAAA  
CACCAAATCCCTGAGAATGGAACATGTTACCCAGGGTATTTCCCGGACTATGAGGAACTGAGGGA  
GCAATTGAGTTCAGTATCTTCATTTGAGAGATTCGAAATATTCCCAAAGAAAAGCTCATGGCCCA  
ACCACACCGTAACCGGAGTATCAGCATCATGCTCCATAATGGGAAAAGCAGTTTTTACAGAAAT  
TTGCTATGGCTGACGGGGAAGAATGGTTTGTACCCAAACCTGAGCAAGTCCTATGTAACAACA  
AAGAGAAAAGAAGTCCTTGTACTATGGGGTGTTCATCACCCGCCTAACATAGGGAACCAAAGGGC  
ACTCTATCATAACAGAAAATGCTTATGTCTCTGTAGTGTCTTCACATTATAGCAGAAGATTCACCCC  
AGAAATAGCCAAAAGACCCAAAGTAAGAGATCAGGAAGGAAGAATCACTACTACTGGACTCTG  
CTGGAACCTGGGGATACAATAATATTTGAGGCAAATGGAAATCTAATAGCGCCATGGTATGCTTT  
TGCACTGAGTAGGAGGCTTTGGATCAGGAATCATCACCTCAAATGCACCAATGGATGAATGTGAT  
GCGAAGTGTCAAACACCTCAGGGAGCTATAAACAGCAGTCTTCCTTTCCAGAATGTACACCCAG  
TCACAATAGGAGAGTGTCCAAAGTATGTGAGGAGTGCAAAATTAAGGATGGTTACAGGACTAAG  
GAACATCCCATCCATTCAATCCAGAGGTTTGTGGAGCCATTGCCGTTTTATTGAAGGGGGG  
TGGACTGGAATGGTAGATGGGTGGTATGGTTATCATCATCAGAATGAGCAAGGATCTGGCTATG  
CTGCAGATCAAAAAGTACACAAAATGCCATTAACGGGATTACAAAACAAGGTCAATTCTGTAATT  
GAGAAAATGAACACTCAATTCACAGCTGTGGCAAAGAGTTCAACAAATTTGAAAGAAAGGATGG  
AAAACCTAAATAAAAAAGTTGATGATGGGTTTCTAGACATTTGGACATATAATGCAGAATGTTGG  
TTCTACTGAAAATGAAAGGACTTTGGATTTCCATGACTCCAATGTGAAGAATCTGTATGAGAAA  
GTAAAAAGCCAAATTAAGAATAATGCCAAAGAAATAGGAAACGGGTGTTTTGAGTTCTATCACAA  
GTGTAACATGAATGCATGGAGAGTGTGAAAAATGGTACCTATGACTATCCAAAATATCCGAAG  
AATCAAAGTTAAACAGGGAGAAAATTTGATGGAGTGAAATTTGGAATCAATGGGAGTATACCAGATT  
CTGGCGATCTACTCAACTGTCCGCACTCCCTGGTTCTTTTGGTCTCCCTGGGGGCAATCAGCT  
CTGGATGTGTTCCAATGGGTCTTTGCAAGTGTAGAAATATGCATCTAAGAGCTCTAAGTTAAAATG  
CTTCTTCGCTCCTATTTATAATATGGTTTGTATTGTTAATTTTGTCTTGTAGAAGAGCTTAATT  
AATCGTTGTTGTTATGAAATACTATTTGTATGAGATGAACTGGTGTAAATGTAATTCATTTACATAAG  
TGGAGTCAGAATCAGAATGTTTCTCCATAACTAACTAGACATGAAGACCTGCCGCGTACAATTG  
TCTTATATTTGAACAACAAAATTTGAACATCTTTGCCACAACCTTTATAAGTGGTTAATATAGCTCA  
AATATATGGTCAAGTTCAATAGATTAATAATGGAATATCAGTTATCGAAATTCATTAACAATCAAC  
TTAACGTTAATACTACTAATTTTATATCATCCCCTTTGATAAATGATAGTACA

Fig. 53

SEQ ID NO: 62

**H1 from A/Brisbane/59/2007 (construct #774)**

CTGGTATATTTATATGTTGTCAAATAACTCAAAAACCATAAAAGTTTAAGTTAGCAAGTGTGTACAT  
TTTTACTTGAACAAAAATATTCACCTACTACTGTTATAAATCATTATTAACATTAGAGTAAAGAAAT  
ATGGATGATAAGAACAAGAGTAGTGATTTTTGACAACAATTTTGTGCAACATTTGAGAAAAATTTT  
GTTGTTCTCTCTTTTCATTGGTCAAAAACAATAGGAGAGAAAAAGGAAGAGGGAGAATAAAAAACA  
TAATGTGAGTATGAGAGAGAAAAGTTGTACAAAAGTTGTACAAAATAGTTGTACAAAATCATTGA  
GGAATTTGACAAAAGCTACACAAAATAAGGGTTAATTGCTGTAATAAATAAGGATGACGCATTAGA  
GAGATGTACCATTAGAGAATTTTTGGCAAGTCATTA AAAAGAAAGAATAAATTTATTTTTAAATTA  
AAGTTGAGTCATTTGATTAACATGTGATTATTTAATGAATTGATGAAAGAGTTGGATTAAGTTGT  
ATTAGTAATTAGAATTTGGTGTCAAATTTAATTTGACATTTGATCTTTTCTATATATTGCCCCATA  
GAGTCAGTTAACTCATTTTTATTTTCATAGATCAAATAAGAGAAAATAACGGTATATTAATCCCTCC  
AAAAAAAAAAAAACGGTATATTTACTAAAAAATCTAAGCCACGTAGGAGGATAACAGGATCCCCGTA  
GGAGGATAACATCCAATCCAACCAATCACACAATCCTGATGAGATAACCCACTTTAAGCCACG  
CATCTGTGGCACATCTACATTATCTAAATCACACATTCTCCACACATCTGAGCCACACAAAAACC  
AATCCACATCTTTATCACCCATTCTATAAAAAATCACACTTTGTGAGTCTACACTTTGATTCCCTTC  
AAACACATACAAAGAGAAGAGACTAATTAATTAATTAATCATCTTGAGAGAAAATGAAAGTAAAACT  
ACTGGTCTGTTATGCACATTTACAGCTACATATGCAGACACAATATGTATAGGCTACCATGCTAA  
CAACTCGACCGACACTGTTGACACAGTACTTGAAGAATGTGACAGTGACACACTCTGTCAACC  
TGCTTGAGAACAGTCACAATGGAAAACCTATGTCTATTA AAAAGGAATAGCCCCACTACAATGGGT  
AATTGCAGCGTTGCCGGTGGATCTTAGGAAACCCAGAATGCGAATTA CTGATTTCCAAGGAGTC  
ATGGTCTACATTGTAGAAAACCAAATCCTGAGAATGGAACATGTTACCCAGGGCATTTCGCTG  
ACTATGAGGAAC TAGGGAGCAATTGAGTTCAATCTTCATTTGAGAGTTGCAAAATTTCCCC  
AAAGAAAGCTCATGGCCCAACCCACACCCGTAACCCGGAGTGTGAGCATCATGCTCCCATATGGGG  
AAAGCAGTTTTTACAGAAATTTGCTATGGCTGACGGGGAAGAATGGTTTGTACCCAAACCTGAGC  
AAGTCTATGCAAACAACAAAGAAAAAGAGTCTTGTACTATGGGGTGTTCATCACCCGCCAAA  
CATAGGTGACCAAAAAGGCCCTCTATCATAACAGAAAATGCTTATGTCTCTGTAGTGTCTTCACATTA  
TAGCAGAAAATTCACCCAGAAAATAGCCAAAAGACCCAAAGTAAGAGATCAAGAAGGAAGAATCA  
ATTACTACTGGACTCTGCTTGAACCCGGGGATACAATAATTTGAGGCAAATGGAATCTAATAG  
CGCCAAGATATGCTTTGCACTGAGTAGAGGCTTTGGATCAGGAATCATCAACTCAATGCACCA  
ATGGATAAATGTGATGCGAAGTGCCAAACACCTCAGGGAGCTATAAACAGCAGTCTTCTTTCCA  
GAACGTACACCCAGTCACAATAGGAGAGTGTCCAAAGTATGTCAGGAGTGCAAAATTAAGGATG  
GTTACAGGACTAAGGAACATCCCATCCATCAATCCAGAGGTTTGTGGAGCCATTGCCGGTTT  
CATTGAAGGGGGGTGGACTGGAATGGTAGATGGTTGGTATGGTTATCATCATCAGAATGAGCAA  
GGATCTGGCTATGCTGCAGATCAAAAAGCACACAAAATGCCATTAATGGGATTACAAACAAGGT  
CAATTCGTGAATTGAGAAAATGAACACTCAATTCACAGCAGTGGGCAAAGAGTTCAACAAATTTGG  
AAAGAAGGATGGA AAACTTGAATAAAAAAGTTGATGATGGGTTTATAGACATTTGGACATATAATG  
CAGAACTGTTGGTTCTACTGGAAAATGAAAGGACTTTGGATTTCCATGACTCCAATGTGAAGAAT  
CTGTATGAGAAAGTAAAAAGCCAGTTAAAGAATAATGCTAAAGAAATAGGAAATGGGTGTTTTGAG  
TTCTATCACAAGTGAACGATGAATGCATGGAGAGTGTAAAGAATGGA ACTTATGACTATCCAAAA  
TATTCGAAGAATCAAAGTTAAACAGGGAGAAAATTTGATGGAGTGAATTTGGAATCAATGGGAGT  
CTATCAGATTCTGGCGATCTACTCAACAGTCGCCAGTCTCTGGTTCTTTTGGTCTCCCTGGGGG  
CAATCAGCTTCTGGATGTGTTCCAATGGGTCTTTACAGTGTAGAATATGCATCTAAGAGCTCTAA  
GTTAAAATGCTTCTTCGTCCTATTTATAATATGGTTTGTATTGTTAATTTTGTCTTGTAGAAGA  
GCTTAATTAATCGTTGTTGTTATGAAATACTATTTGTATGAGATGAACTGGTGAATGTAATTCATT  
TACATAAGTGGAGTCAGAATCAGAATGTTTCTCCATAACTA ACTAGACATGAAGACCTGCCGCG  
TACAATGTCTTATATTTGAACA ACTAAAATTTGAACATCTTTTGCCACA ACTTTATAAGTGGTTAAT  
ATAGCTCAAATATATGGTCAAGTTCAATAGATTAATAATGGAATATCAGTTATCGAAATTCATTA  
CAATCAACTAACGTTATTA ACTACTAATTTTATATCATCCCCTTTGATAAATGATAGTACA

Fig. 54

SEQ ID NO: 63

**H1 from A/Solomon Islands/3/2006 (H1N1) (Construct # 775)**

AGAGGTACCCCGGGCTGGTATATTTATATGTTGTCAAATAACTCAAAAACCATAAAAAGTTTA  
AGTTAGCAAGTGTGTACATTTTTACTTGAACAAAATATTCACCTACTACTGTTATAAATCAT  
TATTAACATTAGAGTAAAGAAATATGGATGATAAGAACAAGAGTAGTGATATTTTGACAAC  
AATTTTGTGCAACATTTGAGAAAATTTGTTGTTCTCTCTTTTCATTGGTCAAAAACAATAG  
AGAGAGAAAAGGAAGAGGGAGAATAAAAACATAATGTGAGTATGAGAGAGAAAGTTGTAC  
AAAAGTTGTACCAAAATAGTTGTACAAATATCATTGAGGAATTTGACAAAAGCTACACAAATA  
AGGGTTAATTGCTGTAATAAATAAGGATGACGCATTAGAGAGATGTACCATTAGAGAATTT  
TTGGCAAGTCATTAAGAAAGAATAAATTATTTTTAAAATTTAAAAGTTGAGTCATTTGATTA  
AACATGTGATTATTTAATGAATTGATGAAAGAGTTGGATTAAAGTTGTATTAGTAATTAGAAT  
TTGGTGTCAAATTTAATTTGACATTTGATCTTTTCTATATATTGCCCATAGAGTCAGTTAA  
CTCATTTTTATATTTTACATAGATCAAATAAGAGAAAATAACGGTATATTAATCCCTCCAAAAAAA  
AAAAACGGTATATTTACTAAAAATCTAAGCCACGTAGGAGGATAACAGGATCCCCGTAGG  
AGGATAACATCCAATCCAACCAATCACAACAATCCTGATGAGATAACCCACTTTAAGCCCAC  
GCATCTGTGGCACATCTACATTATCTAAATCACACATTTCTCCACACATCTGAGCCACACAA  
AAACCAATCCACATCTTTATCACCCATTCTATAAAAAATCACACTTTGTGAGTCTACACTTTG  
ATTCCCTTCAAACACATACAAAGAGAAGAGACTAATTAATTAATTAATCATCTTGAGAGAAAA  
TGAAAGTAAACTACTGGTCTGTTATGCACATTTACAGCTACATATGCAGACACAATATGT  
ATAGGCTACCATGCCAACAACTCAACCGACACTGTTGACACAGTACTTGAGAAGAATGTGA  
CAGTGACACACTCTGTCAACCTGCTTGAGGACAGTCACAATGGAAAATTATGTCTATTA  
GGAATAGCCCCACTACAATTGGGTAATTGCAGCGTTGCCGGATGGATCTTAGGAAACCCA  
GAATGCGAATTACTGATTTCCAGGGAATCATGGTCTACATTGTAGAAAAACCAAATCCTGA  
GAATGGACATGTTACCCAGGGCATTTCGCCGACTATGAGGAACTGAGGGAGCAATTGAG  
TTCAGTATCTTCATTTGAGAGATTCGAAATATTCCCCAAAGAAAGCTCATGGCCCAACCACA  
CCACAACCGGAGTATCAGCATCATGCTCCATAATGGGGAAAGCAGTTTTTACAAAAATTT  
GCTATGGCTGACGGGGAAGAATGGTTTGTACCCAAACCTGAGCAAGTCCATGCAAAACAA  
CAAAGAGAAAAGAAGTCCTTGTACTATGGGGTGTTCATCACCCGCCTAACATAGGTGACCAA  
AGGGCTCTCTATCATAAAGAAAATGCTTATGTCTCTGTAGTGTCTTACATTATAGCAGAAA  
ATTCACCCAGAAAATAGCCAAAAGACCCAAAGTAAGAGATCAAGAAGGAAGAATCAACTAC  
TACTGGACTCTACTTGAACCCGGGGATACAATAATTTGAGGCAAATGGAATCTAATAGC  
GCCAAGATATGCTTTCGCACTGAGTAGAGGCTTTGGATCAGGAATCATCAACTCAAATGCA  
CCAATGGATGAATGTGATGCGAAGTGCCAAACACCTCAGGGAGCTATAAACAGCAGTCTTC  
CTTCCAGAATGTACACCCTGTCACAATAGGAGAGTGTCCAAAGTATGTCAGGAGTGCAAA  
ATTAAGGATGGTTACAGGACTAAGGAACATCCCATCCATTCAATCCAGAGGTTTGTGGGA  
GCCATTGCCGTTTTCATTGAAGGGGGGTGACTGGAATGGTAGATGGTTGGTATGGTTAT  
CATCATCAGAATGAGCAAGGATCTGGCTATGCTGCAGATCAAAAAGCACACAAAATGCCA  
TTAATGGGATTACAAACAAGGTCAATTCTGTAATTGAGAAAATGAACACTCAATTCACAGCT  
GTGGGCAAAGAGTTCAACAAATTTGAAAGAAGGATGGAAAACCTAAATAAAAAAGTTGATG  
ATGGGTTTATAGACATTTGGACATATAATGCAGAATTGTTGGTTCTACTGGAAAATGAAAGG  
ACTTTGGATTTCCATGACTCCAATGTGAAGAATCTGTATGAGAAAAGTAAAAAGCCAATTTAA  
GAATAATGCCAAAGAAAATAGGAAATGGGTGTTTTGAGTTCTATCATAAGTGAACGATGAAT  
GCATGGAGAGTGTAAAAAATGGAACCTTATGACTATCCAAAATATTCCGAAGAATCAAAGTTA  
AACAGGGAGAAAATGATGGAGTGAATTTGGAATCAATGGGAGTCTATCAGATTCTGGCGA  
TCTACTCAACAGTCGCCAGTTCTCTGGTTCTTTTGGTCTCCCTGGGGGCAATCAGCTTCTG  
GATGTGTTCCAATGGGTCTTTGCAGTGTAGAATATGCATCTGAGAGCTCTAAGTTAAATGC  
TTCTTCGTCTCTATTTATAATATGGTTTGTATTGTTAATTTTGTCTTGTAAGAGCTTAA  
TTAATCGTTGTTGTTATGAAATACTATTTGTATGAGATGAACTGGTGAATGTAATTCATTTA  
CATAAGTGGAGTCAGAATCAGAATGTTTCCCTCCATAACTAAGTACATGAAGACCTGCCG  
CGTACAATTGCTTATATTTGAACAATAAATTTGAACATCTTTTGCACAACCTTTATAAGTG  
GTTAATATAGCTCAAATATATGGTCAAGTTCAATAGATTAATAATGGAAATATCAGTTATCGA  
AATTCATTAACAATCAACTTAACGTTATTAACACTAATTTTATATCATCCCCTTTGATAAATG  
ATAGTACA

Fig. 55

SEQ ID NO: 64

**H2 from A/Singapore/1/57 (H2N2) (construct # 780)**

AGAGGTACCCCGGGCTGGTATATTTATATGTTGTCAAATAACTCAAAAACCATAAAAAGTTTAA  
GTTAGCAAGTGTGTACATTTTTACTTGAACAAAAATATTCACCTACTACTGTTATAAATCATTAT  
TAAACATTAGAGTAAAGAAATATGGATGATAAGAACAAGAGTAGTGATTTTTGACAACAATTT  
TGTTGCAACATTTGAGAAAATTTTGTGTTCTCTCTTTTCATTGGTCAAAAACAATAGAGAGAG  
AAAAAGGAAGAGGGAGAATAAAAACATAATGTGAGTATGAGAGAGAAAGTTGTACAAAAGTTG  
TACCAAAATAGTTGTACAAATATCATTGAGGAATTTGACAAAAGCTACACAAATAAGGGTTAAT  
TGCTGTAAATAAATAAGGATGACGCATTAGAGAGATGTACCATTAGAGAATTTTTGGCAAGTC  
ATTAAGAAAGAAAGAATAAATTTATTTTAAAAATTAAGTTGAGTCATTTGATTAACATGTGATT  
TTAATTTGACATTTGATCTTTTCTATATATTGCCCATAGAGTCAGTTAACTCATTTTTATATT  
TCATAGATCAAATAAGAGAAATAACGGTATATTAATCCCTCCAAAAAAAAAAAAACGGTATATTT  
ACTAAAAATCTAAGCCACGTAGGAGGATAACAGGATCCCCGTAGGAGGATAACATCCAATC  
CAACCAATCACACAATCCTGATGAGATAACCCACTTTAAGCCACGCATCTGTGGCACATCT  
ACATTATCTAAATCACACATTTCTCCACACATCTGAGCCACACAAAAACCAATCCACATCTTTA  
TCACCCATTCTATAAAAAATCACACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACA  
AAGAGAAGAGACTAATTAATTAATCATCTTGAGAGAAAAATGGCCATCATTTATCTAATTC  
TCCTGTTACAGCAGTGAGAGGGGACCAAAATATGCATTGGATACCATGCCAATAATTTCCACA  
GAGAAGGTGACACAATTCTAGAGCGGAACGTCACTGTGACTCATGCCAAGGACATTTCTGA  
GAAGACCCATAACGGAAAGTTATGCAAACAAACGGAAATCCCTCCACTTGAAGTAGGGGACT  
GTAGCATTGCCGGATGGCTCCTTGGAATCCAGAATGTGATAGGCTTCTAAGTGTGCCAGAA  
TGGTCCTATATAATGGAGAAAGAAAACCCGAGAGACGGTTTGTGTTATCCAGGCAGCTTCAA  
TGATTATGAAGAATTGAAACATCTCCTCAGCAGCGTGAAACATTTGAGAAAAGTAAAGATTCT  
GCCCAAAGATAGATGGACACAGCATACAACAACCTGGAGGTTACACGGCCTGCGCGGTGTCT  
GGTAATCCATCATTCTTCAGGAACATGGTCTGGCTGACAAAAGAAAAGAAATCAAATTATCCGGTT  
GCCAAATGATCGTACAACAATACAAGCGGAGAACAAATGCTAATAATTTGGGGGGTGACCA  
TCCCAATGATGAGACAGAACAAAGAACATTTGTACCAGAATGTGGGAACCTATGTTTCCGTAG  
GCACATCAACATTGAACAAAAGGTCAACCCACAGACATAGCAACAAAGGCCTAAAGTGAATGGA  
CTAGGAAGTAGAATGGAGTTCTCTTGACCCTATTGGATATGTGGGACACCATAAATTTTGGAG  
AGTACTGGTAATCTAATTGCACCAGAGTATGGATTCAAAATATCGAAAAGAGGTAGTTCAGGG  
ATCATGAAAACAGAAGGAACACTTGAGAACTGTGAGACCAATGCCAACTCCTTTGGGAGC  
AATAAATACAACATTGCCTTTTACAATGTCCACCCACTGACAATAGGTGAGTGCCCAAATA  
TGTAAAATCGGAGAAGTTGGTCTTAGCAACAGGACTAAGGAATGTTCCCAAGATTGAATCAA  
GAGGATTGTTTGGGGCAATAGCTGGTTTTATAGAAGGAGGATGGCAAGGAATGGTTGATGGT  
TGGTATGGATACCATCACAGCAATGACCAGGGATCAGGGTATGCAGCAGACAAAGAATCCAC  
TCAAAGGCATTTGATGGAATCACCAACAAGGTAAATTTCTGTGATTGAAAAGATGAACACCCA  
ATTTGAAGCTGTTGGGAAAGAGTTTCACTAAGTATAGAGAGAAGACTGGAGAACTTGAACAAAA  
GATGGAAGACGGGTTTCTAGATGTGTGGACATACAATGCTGAGCTTCTAGTTCTGATGGAAA  
ATGAGAGGACACTTGACTTTCATGATTCTAATGTCAAGAATCTGTATGATAAAGTCAGAATGC  
AGCTGAGAGACAACGTCAAAGAACTAGGAAATGGATGTTTTGAATTTATCACAAATGTGATG  
ATGAATGCATGAATAGTGTGAAAAACGGGACGTATGATTATCCAAGTATGAAGAAGAGTCTA  
AACTAAATAGAAATGAAATCAAAGGGGTAAAAATGAGCAGCATGGGGTTTATCAAATCCTTG  
CCATTTATGCTACAGTAGCAGGTTCTCTGTCACTGGCAATCATGATGGCTGGGATCTCTTTCT  
GGATGTGCTCCAACGGGCTCTGCAAGTGCAGGATCTGCATATGAGAGCTCTAAGTTAAATG  
CTTCTTCGTCTCCTATTTATAATATGGTTTGTATTGTTAATTTTGTCTTGTAGAAGAGCTTAA  
TTAATCGTTGTTGTTATGAAATACTATTTGTATGAGATGAACTGGTGAATGTAATTCATTTACA  
TAAGTGGAGTCAGAATCAGAATGTTTCCATAACTAAGTACATGAAGACCTGCCGCGTA  
CAATTGTCTTATATTTGAACAACATAAAATGAACATCTTTGCCACAACTTTATAAGTGGTTAAT  
ATAGCTCAAATATATGGTCAAGTTCAATAGATTAATAATGGAAATATCAGTTATCGAAATTCAT  
TAACAATCAACTTAACGTTATTAACTACTAATTTTATATCATCCCCCTTTGATAAATGATAGTACA

Fig. 56

SEQ ID NO: 65

**H5 from A/Anhui/1/2005 (H5N1) (Construct# 781)**

AGAGGTACCCCGGGCTGGTATATTTATATGTTGTCAAATAACTCAAAAACCATAAAAAGTTTAAG  
TTAGCAAGTGTGTACATTTTTACTTGAACAAAAATATTCACCTACTACTGTTATAAATCATTATT  
AAACATTAGAGTAAAGAAATATGGATGATAAGAACAAGAGTAGTGATTTTTGACAACAATTTT  
GTTGCAACATTTGAGAAAATTTTGTGTTCTCTCTTTTCATTGGTCAAAAACAATAGAGAGAGA  
AAAAGGAAGAGGGGAGAATAAAAAACATAATGTGAGTATGAGAGAGAAAGTTGTACAAAAGTTGT  
ACCAAAATAGTTGTACAAATATCATTGAGGAATTTGACAAAAGCTACACAAATAAGGGTTAATT  
GCTGTAATAAATAAGGATGACGCATTAGAGAGATGTACCATTAGAGAATTTTTGGCAAGTCA  
TTAAAAAGAAAGAATAAATTTATTTTTAAAAATTAAGTTGAGTCATTTGATTAACATGTGATTAT  
TTAATGAATTGATGAAAGAGTTGGATTAAGTTGTATTAGTAATTAGAATTTGGTGTCAAATTTA  
ATTTGACATTTGATCTTTTCTATATATTGCCCATAGAGTCAAGTTAACTCATTTTTATATTTTCAT  
AGATCAAATAAGAGAAATAACGGTATATTAATCCCTCCAAAAAACAACGGTATATTTACTA  
AAAAATCTAAGCCACGTAGGAGGATAACAGGATCCCGTAGGAGGATAACATCCAATCCAAC  
CAATCACAACAATCCTGATGAGATAACCCACTTAAGCCCACGCATCTGTGGCACATCTACAT  
TATCTAAATCACACATTTCCACACATCTGAGCCACACAAAAACCAATCCACATCTTTATCAC  
CCATTCTATAAAAAATCACACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAAGA  
GAAGAGACTAATTAATTAATCATCTTGAGAGAAAATGGAGAAAATAGTGCTTCTTCTTGC  
AATAGTCAGCCTTGTAAAAGTGATCAGATTTGCATTGGTTACCATGCAAACAACCTCGACAGA  
GCAGTTGACACAATAATGAAAAAGAACGTTACTGTTACACATGCCAAGACATACTGGAAAA  
GACACACAACGGGAAGCTCTGCGATCTAGATGGAGTGAAGCCTCTGATTTAAGAGATTGTA  
GTGTAGCTGGATGGCTCCTCGGAAACCCAATGTGTGACGAGTTTCATCAATGTGCCGGAATGG  
TCTTACATAGTGGAGAAGGCCAACCCAGCCAATGACCTCTGTTACCCAGGGAATTTCAACGA  
CTATGAAGAAGTGAACACCTATTGAGCAGAATAAACCATTTTTGAGAAAATTCAGATCATCCCC  
AAAAGTTCTTGGTCCGATCATGAAGCCTCATCAGGGGTCAGCTCAGCATGTCCATACCAGGG  
AACGCCCTCCTTTTTCAGAAATGTGGTATGGCTATCAAAAAGAACAATACATACCCAACAATA  
AAGAGAAGCTACAATAATACCAACCAGGAAGATCTTTTGATACTGTGGGGGATTCATCATTCT  
AATGATGCGGCAGAGCAGACAAAAGCTCTCAAAAACCCAACCACTATATTTCCGTTGGGACA  
TCAACACTAAACCAGAGATTGGTACCAAAAATAGCTACTAGATCCAAAGTAAACGGGCAAAAGT  
GGAAGGATGGATTTCTTCTGGACAATTTTAAAACCGAATGATGCAATCAACTTCGAGAGTAAT  
GGAAATTTCAATGCTCCAGAATATGCATACAAAATTGTCAAGAAAGGGGACTCAGCAATTGTT  
AAAAGTGAAGTGGAAATATGGTAACTGCAATACAAAGTGTCAAACCTCAAATAGGGGCGATAAAC  
TCTAGTATGCCATTCACAACATACACCCTCTCACCATCGGGGAATGCCCCAAATATGTGAAA  
TCAAACAAATTAGTCCTTGCAGTGGGCTCAGAAAATAGTCCTCTAAGAGAAAGAAAGAAAA  
AGAGGACTATTTGGAGCTATAGCAGGGTTATAGAGGGAGGATGGCAGGGAATGGTAGATGG  
TTGGTATGGGTACCACCATAGCAATGAGCAGGGGAGTGGGTACGCTGCAGACAAAGAATCCA  
CTCAAAGGCAATAGATGGAGTCACCAATAAGGTCAACTCGATCATTGACAAAATGAACACTC  
AGTTTGAGGCCGTTGGAAGGGAATTAATAACTTAGAAAAGGAGAATAGAGAATTTAAACAAGA  
AAATGGAAGACGGATTCCTAGATGTCTGGACTTATAATGCTGAACCTCTGGTTCTCATGGAAA  
ATGAGAGAACCTAGACTTCCATGATTCAAATGTCAAGAACCCTTACGACAAGGTCCGACTAC  
AGCTTAGGGATAATGCAAAGGAGCTGGGTAACGGTTGTTTCGAGTTCTATCACAATGTGATA  
ATGAATGTATGAAAAGTGTAAAGAAACGGAACGTATGACTACCCGCGATTCAGAAGAAGCAA  
GATTA AAAAGAGAGGAAATAAGTGGAGTAAATTTGGAATCAATAGGAACTTACCAAACTGT  
CAATTTATCAACAGTTGCGAGTTCTCTAGCACTGGCAATCATGGTGGCTGGTCTATCTTTGT  
GGATGTGCTCCAATGGGTCGTTACAATGCAGAATTTGCATTTAAGAGCTCTAAGTTAAAATGC  
TTCTTCGCTCCTATTTATAATATGGTTTGTATTGTTAATTTTGTCTTGTAGAAGACTTAATT  
AATCGTTGTTGTTATGAAATACTATTTGTATGAGATGAACTGGTGTAAATGTAATTCATTTACATA  
AGTGGAGTCAGAATCAGAATGTTTCCCTCCATAACTAAGTACATGAAGACCTGCCGCGTACA  
ATTGTCTTATATTTGAACAACTAAAATTTGAACATCTTTTGGCCAACTTTATAAGTGGTTAATAT  
AGCTCAAATATATGGTCAAGTTCAATAGATTAATAATGGAATATCAGTTATCGAAATTCATTA  
CAATCAACTAACGTTATTAACACTAATTTTATATCATCCCCCTTGATAAATGATAGTACA

Fig. 57

SEQ ID NO: 66

**H5 from A/Vietnam/1194/2004 (H5N1) (Construct # 782)**

AGAGGTACCCCGGGCTGGTATATTTATATGTTGTCAAATAACTCAAAAACCATAAAAAGTTTAAAG  
TTAGCAAGTGTGTACATTTTTACTTGAACAAAAATATTCACCTACTACTGTTATAAATCATTATT  
AAACATTAGAGTAAAGAAATATGGATGATAAGAACAAGAGTAGTGATATTTTGACAACAATTTT  
GTTGCAACATTTGAGAAAATTTGTTGTTCTCTCTTTTCATTGGTCAAAAACAATAGAGAGAGA  
AAAAGGAAGAGGGGAGAATAAAAACATAATGTGAGTATGAGAGAGAAAAGTTGTACAAAAGTTGT  
ACCAAAATAGTTGTACAAATATCATTGAGGAATTTGACAAAAGCTACACAAATAAGGGTTAATT  
GCTGTAATAAATAAGGATGACGCATTAGAGAGATGTACCATTAGAGAATTTTTGGCAAGTCA  
TTAAAAAGAAAGAATAAATTTTAAAAATAAAAGTTGAGTCATTTGATTAACATGTGATTAT  
TTAATGAATTGATGAAAGAGTTGGATTAAGTTGTATTAGTAATTAGAATTTGGTGTCAAATTTA  
ATTTGACATTTGATCTTTTCTATATATTGCCCCATAGAGTCAGTTAACTCATTTTTATATTTTCA  
AGATCAAATAAGAGAAATAACGGTATATTAATCCCTCCAAAAAAAAAAAAACGGTATATTTACTA  
AAAAATCTAAGCCACGTAGGAGGATAACAGGATCCCGTAGGAGGATAACATCCAATCCAAC  
CAATCACAACAACCTGATGAGATAACCCACTTAAAGCCCACGCATCTGTGGCACATCTACAT  
TATCTAAATCACACATTTCCACACATCTGAGCCACACAAAAACCAATCCACATCTTTATCAC  
CCATTCTATAAAAAATCACACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAGA  
GAAGAGACTAATTAATTAATTAATCATCTTGAGAGAAAATGGAGAAAATAGTGCTTCTTTTTGC  
AATAGTCAGTCTTGTAAAAGTGATCAGATTTGCATTGGTTACCATGCAAACAACTCGACAGA  
GCAGGTTGACACAATAATGGAAAAGAACGTTACTGTTACACATGCCCAAGACATACTGGAAAA  
GACACACAATGGGAAGCTCTGCGATCTAGATGGAGTGAAGCCTCTAATTTTGAGAGATTGTAG  
TGTAGCTGGATGGCTCCTCGGAAACCAATGTGTGACGAGTTCATCAATGTGCCGGAATGGT  
CTTACATAGTGGAGAAGGCCAATCCAGTCAATGACCTCTGTTACCCAGGGGATTTCAATGACT  
ATGAAGAATTGAAACACCTATTGAGCAGAATAAACCTTTTGAAGAAAATTCAGATCATCCCCAA  
AAGTTCTTGGTCCAGTCATGAAGCCTCATTGGGGTTCAGCTCAGCATGTCCATACCAGGGAA  
AGTCCCTCTTTTTCAGAAATGTGGTATGGCTTATCAAAAAGAACAGTACATACCCAACAATAAA  
GAGGAGCTACAATAATACCAACCAAGAAGATCTTTTGGTACTGTGGGGGATTCACCATCCTAA  
TGATGCGGCAGAGCAGACAAAGCTCTATCAAAACCCAACCACCTATATTTCCGTTGGGACATC  
TACACTAAACCAGAGATTGGTACCAAGAATAGCTACTAGATCCAAAGTAAACGGGCAAAGTGG  
AAGGATGGAGTCTTCTGACAAATTTTAAAACCGAATGATGCAATCAACTTCGAGAGTAATGG  
AAATTTTATTGCTCCAGAATATGCATACAAAATGTCAAGAAAGGGGACTCAACAATTAAGAAA  
AGTGAATTGGAATATGGTAACTGCAATACCAAGTGTCAAACCTCAATGGGGCGATAAACTCT  
AGCATGCCATTCCACAATATACACCCTCTCACCATCGGGGAATGCCCAAATATGTGAAATCA  
AACAGATTAGTCCTTGGGACTGGGCTCAGAAAATGCCCTCAAAGAGAGAGAAGAAGAAAAAA  
GAGAGGATTATTTGGAGCTATAGCAGTTTTATAGAGGGAGGATGGCAGGGAATGGTAGATG  
GTTGGTATGGGTACCACCATAGCAACGAGCAGGGGAGTGGGTACGCTGCAGACAAAGAATC  
CACTCAAAGGCAATAGATGGAGTCACCAATAAGGTCAACTCGATTATTGACAAAATGAACAC  
TCAGTTTGAGGCCGTTGGAAGGGAATTTAAACAACCTTAGAAAGGAGAATAGAGAATTTAAACAA  
GAAGATGGAAGACGGGTTCTAGATGTCTGGACTTATAATGCTGAACTTCTAGTTCTCATGGA  
AAACGAGAGAACTCTAGACTTTTCATGACTCAAATGTCAAGAACCCTTACGACAAGGTCGGACT  
ACAGCTTAGGGATAATGCAAAGGAGCTGGGTAACGGTTGTTTCGAGTTCTATCATAAATGTGA  
TAATGAATGTATGGAAGTGTAAAGAAACGGAACGTATGACTACCCGCAGTATTCAGAAGAAGC  
AAGACTAAAAAGAGAGGAAATAAGTGGAGTAAAATTGGAATCAATAGGAATTTACCAAATATTG  
TCAATTTATTCTACAGTGGCCAGCTCCCTAGCACTGGCAATCATGGTAGCTGGTCTATCCTTA  
TGGATGTGCTCCAATGGGTGCTTACAATGCAGAAATTTGCATTTAAGAGCTCTAAGTTAAAAATG  
CTTCTTCGTCCTTATAAATATGGTTTGTATTGTTAATTTTGTCTTGTAGAAGAGCTTAA  
TTAATCGTTGTTGTTATGAAATACTATTTGTATGAGATGAACTGGTGTAAATTCATTTACA  
TAAGTGGAGTCAGAATCAGAATGTTTCTCCATAACTAACTAGACATGAAGACCTGCCGCGTA  
CAATTTGCTTATATTTGAACAACATAAATGAACATCTTTTCCACAACCTTTATAAGTGGTTAAT  
ATAGCTCAAATATATGGTCAAGTTCAATAGATTAATAATGGAATATCAGTTATCGAAATTCATT  
ACAATCAACTTAACGTTATTAACACTAATTTTATATCATCCCCTTTGATAAATGATAGTACA

Fig. 58

SEQ ID NO: 67

**H6 from A/Teal/Hong Kong/W312/97 (H6N1) (Construct # 783)**

AGAGGTACCCCGGGCTGGTATATTTATATGTTGTCAAATAACTCAAAAACCATATAAAAGTTTA  
AGTTAGCAAGTGTGTACATTTTTACTTGAACAAAAATTCACCTACTACTGTTATAAATCAT  
TATTAACATTAGAGTAAAGAAATATGGATGATAAGAACAAGAGTAGTGATATTTTGACAACA  
ATTTTGTGCAACATTTGAGAAAAATTTGTTGTTCTCTCTTTTCATTGGTCAAAAACAATAGA  
GAGAGAAAAAGGAAGAGGGGAGAATAAAAAACATAATGTGAGTATGAGAGAGAAAGTTGTACA  
AAAGTTGTACCAAAATAGTTGTACAAATATCATTGAGGAATTTGACAAAAGCTACACAAATAA  
GGGTTAATTGCTGTAATAAATAAGGATGACGCATTAGAGAGATGTACCATTAGAGAATTTT  
TGGCAAGTCATTA AAAAGAAAGAATAAATTTTTTAAAATTA AAAGTTGAGTCATTTGATTA  
ACATGTGATTATTTAATGAATTGATGAAAGAGTTGGATTAAAGTTGTATTAGTAATTAGAATT  
TGGTGTCAAATTTAATTTGACATTTGATCTTTTCTATATATTGCCCATAGAGTCAGTTAAC  
TCATTTTTATATTTCATAGATCAAATAAGAGAAATAACGGTATATTAATCCCTCCAAAAA  
AAACGGTATATTTACTAAAAATCTAAGCCACGTAGGAGGATAACAGGATCCCCGTAGGAG  
GATAACATCCAATCCAACCAATCACAACAATCCTGATGAGATAACCCACTTTAAGCCACGC  
ATCTGTGGCACATCTACATTATCTAAATCACACATCTCCACACATCTGAGCCACACAAAA  
ACCAATCCACATCTTTATCACCCATTCTATAAAAAATCACACTTTGTGAGTCTACACTTTGAT  
TCCCTTCAAACACATACAAAGAGAAGAGACTAATTAATTAATTAATCATCTTGAGAGAAATG  
ATTGCAATCATTGTAATAGCAATACTGGCAGCAGCCGGAAAAGTCAGACAAGATCTGCATTG  
GGTATCATGCCAACAAATCAACAACACAGGTAGATACGATACTTGAGAAGAATGTGACTGT  
CACACACTCAATTGAATTGCTGGAAAATCAGAAGGAAGAAAGATTCTGCAAGATATTGAACA  
AGGCCCTCTCGACTTAAGGGAATGTACCATAGAGGGTTGGATCTTGGGGAATCCCAAT  
GCGACCTATTGCTTGGTGATCAAAGCTGGTCATACATTGTGGAAGACCTACTGCTCAAAA  
CGGGATCTGCTACCCAGGAACCTTAAATGAGGTAGAAGAAGTGAAGGCACTTATTGGATCA  
GGAGAAAGGGTAGAGAGATTTGAGATGTTTCCCAAGCACCTGGCAAGGAGTTGACACC  
AACAGTGAACAACAAGATCCTGCCCTTATTCTACTGGTGCCTTTCTACAGAAACCTCCT  
ATGGATAATAAAAAACCAAGACAGCAGAATATCCAGTAATTAAGGGAATTTACAACAACACTG  
GAACCCAGCCAATCCTCTATTTCTGGGGTGTGCATCATCCTCCTAACCCGACGAGCAAGA  
TACTCTGTATGGCTCTGGTGATCGATACGTTAGAATGGGAACTGAAAGCATGAATTTTGCCA  
AGAGTCCGGAAATTGCGGCAAGGCCTGCTGTGAATGGACAAAGAGGCAGAATTGATTATTA  
TTGGTCCGGTTTTAAAACAGGGGAAACCTTGAATGTGGAATCTAATGGAAATCTAATCGCC  
CCTTGGTATGCATACAAATTTGTCAACACAAATAGTAAAGGAGCCGTCTTCAGGTCAGATTT  
ACCAATCGAGAAGTGGATGCCACATGCCAGACTATTGCAGGGGTTCTAAGGACCAATAAA  
ACATTTCAGAATGTGAGTCCCCTGTGGATAGGAGAATGTCCCAAATACGTGAAAAGTGAAA  
GTCTGAGGCTTGAACCTGGACTAAGAAATGTTCCACAGATTGAACTAGAGGACTCTTCGG  
AGCTATTGCAGGGTTTTATTGAAGGAGGATGGACTGGGATGATAGATGGGTGGTATGGCTAT  
CACCATGAAAATTTCTCAAGGGTCAGGATATGCAGCAGACAGAGAAAGCACTCAAAAGGCTG  
TAAACAGAATTAACAATAAGGTCAATTCATCATCAACAAAAATGAACACACAATTTGAAGCTG  
TCGATCACGAATTTTCAAATCTGGAGAGGAGAATTGACAATCTGAACAAAAGAATGCAAGAT  
GGATTTCTGGATGTTTGGACATACAATGCTGAACTGTTGTTCTTCTTGA AAACGAAAGAAC  
ACTAGACATGCATGACGCAAATGTGAAGAACCTACATGAAAAGGTCAAATCACAACCTAAGG  
GACAATGCTACGATCTTAGGGAATGGTTGCTTTGAATTTGGCATAAGTGTGACAATGAATG  
CATAGAGTCTGTCAAAAATGGTACATATGACTATCCCAAATACCAGACTGAAAGCAAATTA  
ACAGGCTAAAAATAGAATCAGTAAAGCTAGAGAACCTTGGTGTGATCAAATTTCTGCCATT  
TATAGTACGGTATCGAGCAGCCTAGTGTGGTAGGGCTGATCATGGCAATGGGCTTTTGA  
TGTGTTCAAATGGTTCAATGCAGTGCAGGATATGTATATAAGAGCTCTAAGTTAAAATGCTT  
CTTCGCTCCTATTTATAATATGGTTTGTATTGTTAATTTTGTCTTGTAGAAGAGCTTAATT  
AATCGTTGTTGTTATGAAATACTATTTGTATGAGATGAACTGGTGAATGTAATTCATTTACA  
TAAGTGGAGTCAGAATCAGAATGTTTCTCCATAACTAAGACATGAAGACCTGCCGCG  
TACAATTGCTTATATTTGAACAATAAAATGAACATCTTTGCCACAACCTTTAAGTGGTT  
AATATAGCTCAAATATATGGTCAAGTTCAATAGATTAATAATGGAAATATCAGTTATCGAAAT  
TCATTAACAATCAACTAACGTTATTA ACTACTAATTTTATATCATCCCCTTTGATAAATGATA  
GTACA

Fig. 59

SEQ ID NO: 68

H9 from A/Hong Kong/1073/99 (H9N2) (Construct # 785)

AGAGGTACCCCGGGCTGGTATATTTATATGTTGTCAAATAACTCAAAAACCATAAAAAGTTTAA  
GTTAGCAAGTGTGTACATTTTTACTTGAACAAAAATATTCACCTACTACTGTTATAAATCATT  
TTAAACATTAGAGTAAAGAAATATGGATGATAAGAACAAGAGTAGTGATATTTTGACAACAAT  
TTTGTGCAACATTTGAGAAAAATTTGTTGTTCTCTCTTTTCATTGGTCAAAAACAATAGAGAG  
AGAAAAAGGAAGAGGGAGAATAAAAAACATAATGTGAGTATGAGAGAGAAAGTTGTACAAAAG  
TTGTACCAAATAGTTGTACAAATATCATTGAGGAATTTGACAAAAGCTACACAAATAAGGGT  
TAATTGCTGTAATAAATAAGGATGACGCATTAGAGAGATGTACCATTAGAGAATTTTTGGCA  
AGTCATTAAGAAGAAATAAATTAATTTTTAAAAATTAAGTTGAGTCATTTGATTAACATG  
TGATTATTAATGAATTGATGAAAGAGTTGGATTAAGTTGATTAGTAATTAGAATTTGGTGT  
CAAATTTAATTTGACATTTGATCTTTTCCATATATATTGCCCATAGAGTCAGTTAACTCATTTT  
TATATTTTATAGATCAAATAAGAGAAATAACGGTATATTAATCCCTCCAAAAAACAACGG  
TATATTTACTAAAAATCTAAGCCACGTAGGAGGATAACAGGATCCCCGTAGGAGGATAACA  
TCCAATCCAACCAATCACAACAATCCTGATGAGATAACCCACTTAAGCCCACGCATCTGTG  
GCACATCTACATTATCTAAATCACACATTCTCCACACATCTGAGCCACACAAAAACCAATCC  
ACATCTTTATCACCCATTCTATAAAAAATCACACTTTGTGAGTCTACACTTTGATTCCCTCAA  
ACACATACAAAGAGAAGAGACTAATTAATTAATTAATCATCTTGAGAGAAAATGGAACAATA  
TCACTAATAACTATACTACTAGTAGTAACAGCAAGCAATGCAGATAAAATCTGCATCGGCCA  
CCAGTCAACAAACTCCACAGAAACTGTGGACACGCTAACAGAAAACCAATGTTCCCTGTGACAC  
ATGCCAAAGAATTGCTCCACACAGAGCATAATGGAATGCTGTGTGCAACAAGCCTGGGACA  
TCCCCTCATTCTAGACACATGCACTATTGAAGGACTAGTCTATGGCAACCCCTTCTGTGACC  
TGCTGTTGGGAGGAAGAGAATGGTCCTACATCGTCAAAGATCATCAGCTGTAATGGAAC  
GTGTTACCCTGGGAATGTAGAAAACCTAGAGGAACCTCAGGACACTTTTTAGTTCGCTAGTT  
CCTACCAAAGAATCAAATCTTCCAGACACAACCTGGAATGTGACTTACACTGGAACAAGC  
AGAGCATGTTCAAGGTTCACTTACAGGAGTATGAGATGGCTGACTCAAAAGAGCGGTTTTTA  
CCCTGTTCAAGACGCCAATACACAAATAACAGGGGAAAGAGCATTCTTTTCGTGTGGGGC  
ATACATCACCCACCCACTATACCGAGCAAACAATTTGTACATAAGAAACGACACAACAAC  
AAGCGTGACAACAGAAGATTTGAATAGGACCTTCAAACAGTGATAGGGCCAAGGCCCTT  
GTCAATGGTCTGCAGGGAAGAATTGATTATTGTTGTCGGTACTAAAACCAGGCCAAACATT  
GCGAGTAGCATCCAATGGGAATCTAATTGCTCCATGGTATGGACACGTTCTTTCAGGAGGG  
AGCCATGGAAGAATCCTGAAGACTGATTTAAAAGGTGGTAATTGTGTAGTGAATGTCAGAC  
TGAAAAGGTGGCTTAAACAGTACATTGCCATTCCACAATATCAGTAAATATGCATTTGGAAC  
CTGCCCAAATATGTAAGAGTTAATAGTCTCAAACCTGGCAGTCCGGTCTGAGGAACGTGCC  
GCTAGATCAAGTAGAGGACTATTTGGAGCCATAGCTGGATTATAGAAGGAGGTTGGCCAG  
GACTAGTCGCTGGCTGGTATGGTTTTCCAGCATTCAAATGATCAAGGGGTTGGTATGGCTGC  
AGATAGGGATTCAACTCAAAGGCAATTGATAAAATAACATCCAAGTGAATAATATAGTCGA  
CAAGATGAACAAGCAATATGAAATAATTGATCATGAATTTAGTGAGGTTGAACTAGACTCAA  
TATGATCAATAATAAGATTGATGACCAAATACAAGACGTATGGGCATATAATGCAGAATTGCT  
AGTACTACTTGAAAAACAAAAACACTCGATGAGCATGATGCGAACGTGAACAATCTATATAA  
CAAGGTGAAGAGGGCACTGGGCTCCAATGCTATGGAAGATGGGAAAGGCTGTTTCGAGCTA  
TACCATAAATGTGATGATCAGTGCATGGAACAATTCGGAACGGGACCTATAATAGGAGAAA  
GTATAGAGAGGAATCAAGACTAGAAAGGCAGAAAATAGAGGGGTTAAGCTGGAATCTGAG  
GGAACCTTACAAAATCCTCACCATTTATTCGACTGTCCCTCATCTCTTGTGCTTGAATGGG  
GTTTGTGCTTCTGTTCTGGGCCATGTCCAATGGATCTTGCAGATGCAACATTTGTATAT  
AAGAGCTCTAAGTTAAATGCTTCTCGTCTCCTATTTATAATATGGTTTGTATTGTTAATTT  
TGTTCTGTAGAAGAGCTTAATTAATCGTTGTTGTTATGAAATACTATTTGTATGAGATGAAC  
GGTGAATGTAATTCATTTACATAAGTGGAGTCAGAAATCAGAAATGTTTCCATAACTAACT  
AGACATGAAGACCTGCCGCTACAATTGCTTATATTTGAACAACAAAATTGAACATCTTTT  
GCCACAACCTTTATAAGTGGTTAATATAGCTCAAATATATGGTCAAGTTCAATAGATTAATAA  
GGAAATATCAGTTATCGAAATTCATTAACAATCAACTTAACGTTATTAACACTAATTTTATAT  
CATCCCCTTGTATAAATGATAGTACA

Fig. 60

SEQ ID NO: 69

H3 from A/Brisbane/10/2007 (H3N2)

AGAGGTACCCCGGGCTGGTATATTTATATGTTGTCAAATAACTCAAAAACCATAAAAAGTTTAAAGT  
TAGCAAGTGTGTACATTTTTACTTGAACAAAAATATTCACCTACTACTGTTATAAATCATTATTTAA  
ACATTAGAGTAAAGAAATATGGATGATAAGAACAAGAGTAGTGATATTTTGACAACAATTTTGTT  
GCAACATTTGAGAAAATTTTGTTGTTCTCTCTTTTCATTGGTCAAAAACAATAGAGAGAGAAAA  
GGAAGAGGGAGAATAAAAACATAATGTGAGTATGAGAGAGAAAAGTTGTACAAAAGTTGTACCAA  
AATAGTTGTACAAATATCATTGAGGAATTTGACAAAAGCTACACAAATAAGGGTTAATTGCTGTA  
AATAAATAAGGATGACGCATTAGAGAGATGTACCATTAGAGAATTTTTGGCAAGTCATTAATAAAG  
AAAGAATAAATTAATTTTAAAATTAAGTTGAGTCATTTGATTAACATGTGATTATTTAATGAAT  
TGATGAAAGAGTTGGATTAAGTTGTATTAGTAATTAGAATTTGGTGTCAAATTTAATTTGACATT  
TGATCTTTTTCTATATATTGCCCATAGAGTCAGTTAACTCATTTTTATTTTCATAGATCAAATA  
AGAGAAATAACGGTATATTAATCCCTCCAAAAAAAAAAAAACGGTATATTTACTAAAAAATCTAAG  
CCACGTAGGAGGATAACAGGATCCCCGTAGGAGGATAACATCCAATCCAACCAATCACAACAA  
TCCTGATGAGATAACCCACTTTAAGCCACGCATCTGTGGCACATCTACATTATCTAAATCACA  
CATTCTTCCACACATCTGAGCCACACAAAAACCAATCCACATCTTTATCACCCATTCTATAAAAA  
ATCACACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAAGAGAAAGAGACTAATTA  
TTAATTAATCATCTTGAGAGAAAATGAAGACTATCATTGCTTTGAGCTACATTCTATGTCTGGTT  
TTCACTCAAAAACCTCCCGGAAATGACAACAGCACGGCAACGCTGTGCCTTGGGCACCATGCA  
GTACCAAACGGAACGATAGTGAACAACATCACGAATGACCAAATTGAAGTTACTAATGCTACTG  
AGCTGGTTCAGAGTTCCTCAACAGGTGAAATATGCGACAGTCCCTCATCAGATCCTTGATGGAG  
AAAACGACACTAATAGATGCTCTATTGGGAGACCCTCAGTGTGATGGCTTCCAAAATAAGAA  
ATGGGACCTTTTTGTTGAACGCAGCAAAGCCTACAGCAACTGTTACCCCTTATGATGTGCCGGAT  
TATGCCTCCCTTAGGTCACTAGTTGCCTCATCCGGCACACTGGAGTTTAAACAATGAAAGTTTCA  
ATTGGACTGGAGTCACTCAAAACGGAACAAGCTCTGCTTGCATAAGGAGATCTAATAACAGTTT  
CTTTAGTAGATTGAATGGTTGACCCACTTAAAATCAAATACCCAGCATTGAACGTGACTATGC  
CAAAACAATGAAAAATTTGACAAAATTGTACATTTGGGGGTTTACCACCCGGTACGGCAATGA  
CCAAATCTTCTGTATGCTCAAGCATCAGGAAGAATCACAGTCTCTACCAAAGAAGCCAACAA  
ACTGTAATCCCGAATATCGGATCTAGACCCAGAGTAAGGAATATCCCCAGCAGAATAAGCATCT  
ATTGGACAATAGTAAAACCGGGAGACATACTTTTGATTAACAGCACAGGGAATCTAATTGCTCC  
TAGGGGTTACTTCAAATACGAAGTGGGAAAAGCTCAATAATGAGATCAGATGCACCCATTGG  
CAAATGCAATTCTGAATGCATCACTCCAAACGGAAGCATTCCCAATGACAAACCATTCCAAAAT  
GTAAACAGGATCACATACGGGGCCTGTCCAGATATGTTAAGCAAACACTCTGAAATTGGCA  
ACAGGGATGCGAAATGTACCAGAGAAACAACTAGAGGCATATTTGGCGCAATCGCGGGTTTT  
ATAGAAAATGGTTGGGAGGGAATGGTGGATGGTTGGTATGGTTTCAGGCATCAAAATCTGAG  
GGAATAGGACAAGCAGCAGATCTCAAAGCACTCAAGCAGCAATCGATCAAATCAATGGGAAG  
CTGAATAGTGTGATCGGGAAAACCAACGAGAAATTCATCAGATTGAAAAAGAGTTCTCAGAAG  
TCGAAGGGAGAATCCAGGACCTTGAGAAATATGTTGAGGACACCAAATAGATCTCTGGTCAT  
ACAACGCGGAGCTTCTTGTGCTTGGGAGAACCAACATACAATTGATCTAACTGACTCAGAAAT  
GAACAACTGTTTGA AAAAACAAGAAGCAACTGAGGGAAAATGCTGAGGATATGGGCAATGG  
TTGTTTCAAATATACCACAAATGTGACAATGCCTGCATAGGATCAATCAGAAATGGAACCTTATG  
ACCACGATGTATACAGAGATGAAGCATTAAACAACCGGTTCCAGATCAAGGGCGTTGAGCTGA  
AGTCAGGATACAAAGATTGGATACTATGGATTTCTTTGCCATATCATGTTTTTTGCTTTGTGTT  
GCTTTGTTGGGGTTCATCATGTGGGCCTGCCAAAAGGCAACATTAGGTGCAACATTTGCATTT  
GAGAGCTCTAAGTTAAATGCTTCTCGTCTCCTATTTATAATATGGTTTGTATTGTTAATTTTG  
TTCTTGTAAGAGACTTAATTAATCGTTGTTGTTATGAAATACTATTTGTATGAGATGAACTGGT  
GTAATGTAATTCATTTACATAAGTGGAGTCAGAATCAGAATGTTTCTCCATAACTAAGTACAA  
TGAAGACCTGCCGCTACAATTGCTTATATTTGAACAACATAAAATTTGAACATCTTTTCCACAA  
CTTTATAAGTGGTTAATATAGCTCAAATATATGGTCAAGTTCAATAGATTAATAATGGAAATATCA  
GTTATCGAAATTCATTAACAATCAACTTAACGTTATTAACTACTAATTTTATATCATCCCCTTTGA  
TAAATGATAGTACA

**Fig. 61**

SEQ ID NO: 70

**H3 from A/Wisconsin/67/2005 (H3N2)**

AGAGGTACCCCGGGCTGGTATATTTATATGTTGTCAAATAACTCAAAAACCATAAAAAGTTTAA  
GTTAGCAAGTGTGTACATTTTTACTTGAACAAAAATATTCACCTACTACTGTTATAAATCATT  
TTAAACATTAGAGTAAAGAAATATGGATGATAAGAACAAGAGTAGTGATATTTTGACAACAAT  
TTTGTGCAACATTTGAGAAAAATTTGTTGTTCTCTCTTTTCATTGGTCAAAAACAATAGAGAG  
AGAAAAAGGAAGAGGGAGAATAAAAACATAATGTGAGTATGAGAGAGAAAGTTGTACAAAAG  
TTGTACCAAAATAGTTGTACAAATATCATTGAGGAATTTGACAAAAGCTACACAAATAAGGGT  
TAATTGCTGTAAATAAATAAGGATGACGCATTAGAGAGATGTACCATTAGAGAAATTTTGGCA  
AGTCATTAAGAAAGAAAGAATAAATTATTTTTAAAAATAAAAGTTGAGTCATTTGATTAACATGT  
GATTATTAATGAATTGATGAAAGAGTTGGATTAAGTTGATTAGTAATTAGAATTTGGTGTG  
AAATTTAATTTGACATTTGATCTTTTCCATATATATTGCCCATAGAGTCAGTTAACTCATTTTTA  
TATTTCATAGATCAAATAAGAGAAATAACGGTATATTAATCCCTCCAAAAAAAAAAAAACGGTAT  
ATTTACTAAAAAATCTAAGCCACGTAGGAGGATAACAGGATCCCGTAGGAGGATAACATCC  
AATCCAACCAATCACAACAATCCTGATGAGATAACCCACTTTAAGCCACGCATCTGTGGCA  
CATCTACATTATCTAAATCACACATTCTCCACACATCTGAGCCACACAAAAACCAATCCACA  
TCTTTATCACCCATTCTATAAAAAATCACACTTTGTGAGTCTACACTTTGATTCCCTCAAACA  
CATACAAGAGAAGAGACTAATTAATTAATCATCTTGAGAGAAAATGAAGACTATCATT  
GCTTTGAGCTACATTTCTATGTCTGGTTTTCACTCAAAAACCTCCCGGAAATGACAACAGCAC  
GGCAACGCTGTGCCCTTGGGCACCATGCAGTACCAAACGGAACGATAGTGAAAACAAATCAGC  
AATGACCAAATTGAAGTTACTAATGCTACTGAGCTGGTTCAGAGTTCCTCAACAGGTGGAAT  
ATGCGACAGTCTCATCAGATCCTTGATGGAGAAAACCTGCACACTAATAGATGCTCTATTGG  
GAGACCCTCAGTGTGATGGCTTCCAAAATAAGAAATGGGACCTTTTTGTTGAACGCAGCAAA  
GCCTACAGCAACTGTTACCCTTATGATGTGCCGGATTATGCCTCCCTTAGGTCAGTTGC  
CTCATCCGGCACACTGGAGTTAACGATGAAAGTTTCAATTGGACTGGAGTCACTCAAAATG  
GAACAAGCTCTGCTTGCAAAAGGAGATCTAATAACAGTTTCTTTAGTAGATTGAATTGGTTGA  
CCCATTAAAAATCAAATACCCAGCATTGAACGTGACTATGCCAAACAATGAAAAATTTGACA  
AATGTACATTTGGGGGTTCCACCACCCGGTACGGACAATGACCAAATCTTCTGCATGCT  
CAAGCATCAGGAAGAATCACAGTCTCTACCAAAGAAGCCAACAACTGTAATCCCGAATAT  
CGGATCTAGACCCAGAATAAGGAATATCCCCAGCAGAATAAGCATCTATTGGACAATAGTAA  
AACCGGGAGACATACTTTTGATTAACAGCACAGGGAATCTAATTGCTCCTAGGGGTTACTTC  
AAAATACGAAGTGGGAAAAGCTCAATAATGAGATCAGATGCACCCATTGGCAAATGCAATTC  
TGAATGCATCACTCAAATGGAAGCATTCCAATGACAAACCATTTCAAATGTAAACAGGAT  
CACATATGGGGCCTGTCCCAGATATGTTAAGCAAAAACACTCTGAAATTGGCAACAGGGATGC  
GAAATGTACCAGAGAAACAACTAGAGGCATATTTGGCGCAATCGCGGGTTTCATAGAAAAT  
GGTTGGGAGGGAATGGTGGATGGTTGGTACGGTTTCAGGCATCAAATTTCTGAGGGAATAG  
GACAAGCAGCAGATCTCAAAGCACTCAAGCAGCAATCAATCAAATCAATGGGAAGCTGAAT  
AGGTTGATCGGGAAAACCAACGAGAAATTCATCAGATTGAAAAAGAGTTCTCAGAAGTAGA  
AGGGAGAATCCAGGACCTCGAGAAATATGTTGAGGACACTAAAATAGATCTCTGGTCATACA  
ACGCGGAGCTTCTTGTGCCCTGGAGAACCAACATACAATTGATCTAACTGACTCAGAAATG  
AACAAACTGTTTGAAGAACAAGAAGCAACTGAGGGAAAATGCTGAGGATATGGGCAATGG  
TTGTTTCAAATATAACCACAAATGTGACAATGCCTGCATAGGATCAATCAGAAATGGAACCTTA  
TGACCATGATGTATACAGAGATGAAGCATTAAACAACCGGTTCCAGATCAAAGGCCTTGAGC  
TGAAGTCAGGATACAAAGATTGGATACTATGGATTTCCCTTGGCCATATCATGTTTTTGTCTT  
GTGTTGCTTTGTTGGGGTTTCATGTGGGCTGCCAAAAAGGCAACATTAGGTGCAACATT  
TGCATTTGAGAGCTCTAAGTTAAATGCTTCTCGTCTCCTATTTATAATATGGTTGTTATTG  
TTAATTTTGTCTTGTAGAAGAGCTTAATTAATCGTTGTTGTTATGAAATACTATTTGTATGAG  
ATGAACTGGTGAATGTAATTCATTTACATAAGTGGAGTCAGAATCAGAATGTTTCCCTCCATA  
ACTAACTAGACATGAAGACCTGCCGCTACAATTGTCTTATATTTGAACAACATAAAATGAAC  
ATCTTTTGCCACAACCTTATAAGTGGTTAATATAGCTCAAATATATGGTCAAGTTCAATAGATT  
ATAATGGAAATATCAGTTATCGAAATTCATTAACAATCAACTTAACGTTATTACTACTAATTT  
TATATCATCCCCTTTGATAAATGATAGTACA

Fig. 62

SEQ ID NO: 71

H7 from A/Equine/Prague/56 (H7N7)

AGAGGTACCCCGGGCTGGTATATTTATATGTTGTCAAATAACTCAAAAACCATAAAAGTTTAAAG  
TTAGCAAGTGTGTACATTTTTACTTTGAACAAAAATATTCACCTACTACTGTTATAAATCATTATT  
AAACATTAGAGTAAAGAAATATGGATGATAAGAACAAGAGTAGTGATATTTTGACAACAATTTT  
GTTGCAACATTTGAGAAAATTTTGTGTTCTCTCTTTTCATTGGTCAAAAACAATAGAGAGAGA  
AAAAGGAAGAGGGAGAATAAAAACATAATGTGAGTATGAGAGAGAAAAGTTGTACAAAAGTTGT  
ACCAAAATAGTTGTACAAATATCATTGAGGAATTTGACAAAAGCTACACAAAATAAGGGTTAATT  
GCTGTAATAAATAAGGATGACGCATTAGAGAGATGTACCATTAGAGAATTTTTGGCAAGTCA  
TTAAAAGAAAAGAATAAATTTTTTAAAATTTAAAAGTTGAGTCATTTGATTAACATGTGATTAT  
TTAATGAATTGATGAAAGAGTTGGATTAAGTTGTATTAGTAATTAGAATTTGGTGTCAAATTTA  
ATTTGACATTTGATCTTTTCTATATATTGCCCATAGAGTCAGTTAACTCATTTTTATATTTCA  
TAGATCAAATAAGAGAAATAACGGTATATTAATCCCTCCAAAAAAAAAAAAACGGTATATTTACT  
AAAAATCTAAGCCACGTAGGAGGATAACAGGATCCCGTAGGAGGATAACATCCAATCCAA  
CCAATCACAACAATCCTGATGAGATAACCCACTTTAAGCCCACGCATCTGTGGCACATCTACA  
TTATCTAAATCACACATTCTCCACACATCTGAGCCACACAAAAACCAATCCACATCTTTATCA  
CCCATTCTATAAAAAATCACACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAAG  
AGAAGAGACTAATTAATTAATTAATCATCTTGAGAGAAAATGAACACTCAAATTCTAATATTAG  
CCACTTCGGCATTCTTCTATGTACGTGCAGATAAAAATCTGCCTAGGACATCATGCTGTGTCTA  
ATGGAACCAAAGTAGACACCCTTACTGAAAAAGGAATAGAAGTTGTCAATGCAACAGAAACAG  
TTGAACAAACAAACATCCCTAAGATCTGCTCAAAGGAAAACAGACTGTTGACCTTGGTCAAT  
GTGGATTACTAGGGACCGTTATTGGTCTCCCAATGTGACCAATTTCTTGAGTTCTCTGCTA  
ATTTAATAGTTGAAAGAAGGGAAGGTAATGACATTTGTTATCCAGGCAAATTTGACAATGAAGA  
AACATTGAGAAAAATACTCAGAAAAATCCGGAGGAATTTAAAAGGAGAATATGGGATTCACATA  
TACCGGAGTGAGAACCAATGGAGAGACTAGCGCATGTAGAAGGTCAAGATCTTCTTTTATG  
CAGAGATGAAATGGCTTCTATCCAGCACAGACAATGGGACATTTCCACAAATGACAAAGTCTC  
ACAAGAACACTAAGAAGGTACCAGCTCTGATAATCTGGGGAATCCACCACTCAGGATCAACT  
ACTGAACAGACTAGATTATATGGAAGTGGGAATAAATTGATAACAGTTTGGAGTTCCAAATAC  
CAACAATCTTTTGTCCCAAATCCTGGACCAAGACCGCAAATGAATGGTCAATCAGGAAGAATT  
GACTTTCACTGGCTGATGCTAGATCCCAATGATACTGTCACTTTCACTTTTAAATGGGGCCTTT  
ATAGCACCTGACCGCGCCAGTTTTCTAAGAGGTAATCTCTAGGAATCCAAAGTGATGCACAA  
CTTGACAATAATTGTGAAGGTGAATGCTATCATATTGGAGTACTATAATTAGCAACTTGCCCT  
TTCAAACATTAATAGTAGGGCAATCGGAAAATGCCCCAGATACGTGAAGCAGAAGAGCTTAA  
TGCTAGCAACAGGAATGAAAAATGTTCTGAAAGTCTCTGCACATAAAACAACTAACTCATCACA  
TGCGCAAAAAAAGAGGTTTATTTGGTGAATAGCAGGATTCATTGAAAATGGGTGGGAAGGAT  
TAATAGACGGATGGTATGGATATAAGCATCAGAATGCACAAGGAGAAGGGACTGCTGCAGAC  
TACAAAAGTACACAATCTGCTATCAACCAAATAACCGGAAAAATTGAACAGACTAATAGAAAAAA  
CCAACCAGCAATTCGAACATAATAGATAATGAGTTCAATGAAATGAAAAACAATTTGGCAATGT  
TATTAACTGGACTAGAGATTCTATCATCGAAGTATGGTCATATAATGCAGAGTTCTCCTGATGC  
AGTGGAGAATCAACACACTATTGATTTAACTGACTCAGAAATGAACAACTATATGAAAAGGTA  
AGAAGACAACACTGAGAGAAAATGCTGAGGAAGATGGTAATGGCTGTTTTGAAATATTCCACCAA  
TGTGACAATGATTGCATGGCCAGCATTAGAAAACAACACATATGACCATAAAAAATACAGAAAA  
GAGGCAATACAAAACAGAATCCAGATTGACGCAGTAAAGTTGAGCAGTGGTTACAAAGATATA  
ATACTTTGGTTTAGCTTCGGGGCATCATGTTTCTTATTTCTTGCCATTGCAATGGGTCTTGTTT  
TCATATGTATAAAAAATGGAACATGCGGTGCACTATTTGTATATAAGAGCTCTAAGTTAAAAT  
GCTTCTTCGTCTCCTATTTATAATATGGTTTGTATTGTTAATTTTGTCTTGTAGAAGAGCTTA  
ATTAATCGTTGTTGTTATGAAATACTATTTGTATGAGATGAACTGGTGAATGTAATTCATTTAC  
ATAAGTGGAGTCAGAATCAGAATGTTTCTCCATAACTAACTAGACATGAAGACCTGCCGCGT  
ACAATTGTCTTATATTTGAACAATAAAATTTGAACATCTTTTGCCACAACCTTTATAAGTGGTTAA  
TATAGCTCAAATATATGGTCAAGTTCAATAGATTAATAATGGAATATCAGTTATCGAAATTCAT  
TAACAATCAACTAACGTTATTAACACTAATTTTATATCATCCCTTTGATAAATGATAGTACA

Fig. 63

SEQ ID NO: 72

HA from B/Malaysia/2506/2004

AGAGGTACCCCGGGCTGGTATATTTATATGTTGTCAAATAACTCAAAAACCATAAAAAGTTTAAG  
TTAGCAAGTGTGTACATTTTTACTTGAACAAAAATATTCACCTACTACTGTTATAAATCATTATTA  
AACATTAGAGTAAAGAAATATGGATGATAAGAACAAGAGTAGTGATATTTTGACAACAATTTTGT  
TGCAACATTTGAGAAAATTTTGTGTTCTCTCTTTTCATTGGTCAAAAACAATAGAGAGAGAAAA  
AGGAAGAGGGAGAATAAAAACATAATGTGAGTATGAGAGAGAAAAGTTGTACAAAAGTTGTACC  
AAAATAGTTGTACAAATACATTGAGGAATTTGACAAAAGCTACACAAATAAGGGTTAATTGCTG  
TAAATAAATAAGGATGACGCATTAGAGAGATGTACCATTAGAGAATTTTGGCAAGTCATTA  
AAGAAAGAATAAAATTTTTTAAAATTTAAAAGTTGAGTCATTTGATTAACATGTGATTATTTAAT  
GAATTGATGAAAGAGTTGGATTAAGTTGTATTAGTAATTAGAATTTGGTGTCAAATTTAATTTG  
ACATTTGATCTTTTCTATATATTGCCCATAGAGTCAGTTAACTCATTTTTATATTTTCATAGATC  
AAATAAGAGAAATAACGGTATATTAATCCCTCCAAAAAAAAAAAAACGGTATATTTACTAAAAAAT  
CTAAGCCACGTAGGAGGATAACAGGATCCCCGTAGGAGGATAACATCCAATCCAACCAATCAC  
ACAATCCTGATGAGATAACCCACTTTAAGCCCACGCATCTGTGGCACATCTACATTATCTAAA  
TCACACATTCTCCACACATCTGAGCCACACAAAACCAATCCACATCTTTATCACCCATTCTAT  
AAAAATCACACTTTGTGAGTCTACACTTTGATTCCCTTCAAACACATACAAAGAGAAGAGACT  
AATTAATTAATTAATCATCTTGAGAGAAAAAGGGAATAATTGTACTACTCATGGTAGTAACA  
TCCAATGCAGATCGAATCTGCACTGGGATAACATCGTCAAACCTACCACATGTTGTCAAACCTG  
CTACTCAAGGGGAGGTCAATGTGACTGGTGAATACCACTGACAACAACACCCACCAAAATCTC  
ATTTTGCAAACTCAAAGGAACAGAAACCAGAGGGAAACTATGCCAAAAATGCCCTCAACTGCA  
CAGATCTGGACGTGGCCTTGGGCAGACCAAAATGCACGGGGAACATACCCTCGGCAAGAGTT  
TCAATACTCCATGAAGTCAGACCTGTTACATCTGGGTGCTTTCCTATAATGCACGACAGAACAA  
AAATTAGACAGCTGCCTAACTTCTCAGAGGATACGAACATATCAGGTTATCAACTCATAACGT  
TATCAATGCAGAAAATGCACCAGGAGGACCCTACAAAATTGGAACCTCAGGGTCTTGCCCTAA  
CGTTACCAATGGAAACGGATTTTTCGCAACAATGGCTTGGGCCGTCCCAAAAAACGACAACAA  
CAAAACAGCAACAAATTCATTAACAATAGAAGTACCATACATTTGTACAGAAGGAGAAGACCAA  
ATTACCGTTTGGGGGTTCCACTCTGATAACGAAACCCAAATGGCAAAGCTCTATGGGGACTCA  
AAGCCCAGAAAGTTCACCTCATCTGCCAACGGAGTGACCACACATTACGTTTACAGATTGGT  
GGCTTCCCAATCAAACAGAAAGACGGAGGACTACCACAAAGCGGTAGAATTGTTGTTGATTAC  
ATGGTGCAAAAATCTGGGAAAACAGGAACAATTACCTATCAAAGAGGTATTTTATTGCCTCAA  
AAGTGTGGTGCGCAAGTGGCAGGAGCAAGGTAATAAAAGGATCGTTGCCTTTAATTGGAGAAG  
CAGATTGCCTCCACGAAAAATACGGTGGATTAACAAAAGCAAGCCTTACTACACAGGGGAAC  
ATGCAAAGGCCATAGGAAATTCGCCAATATGGGTGAAAACACCCCTTGAAGCTGGCCAATGGAA  
CCAAATATAGACCTCCTGCAAACTATTAAGGAAAGGGTTTCTTCGGAGCTATTGCTGGTTT  
CTTAGAAGGAGGATGGGAAGGAATGATTGCAGGTTGGCACGGATACACATCCCATGGGGCAC  
ATGGAGTAGCGGTGGCAGCAGACCTTAAGAGCACTCAAGAGGCCATAAACAAGATAACAAAA  
ATCTCAACTCTTTGAGTGAGCTGGAAGTAAAGAATCTTCAAAGACTAAGCGGTGCCATGGATG  
AACTCCACAACGAAATACTAGAACTAGACGAGAAAGTGGATGATCTCAGAGCTGATACAATAA  
GCTCACAATAAGAACTCGCAGTCCTGCTTCCAATGAAGGAATAATAAACAGTGAAGATGAGC  
ATCTCTTGGCGCTTGAAGAAAAGCTGAAGAAAATGCTGGGCCCTCTGCTGTAGAGATAGGGA  
ATGGATGCTTTGAAACCAAAACACAAGTGAACCCAGACCTGTCTCGACAGAATAGCTGCTGGTA  
CCTTTGATGCAGGAGAATTTTCTCTCCCACCTTTTGATTCACTGAATATTACTGCTGCATCTTTA  
AATGACGATGGATTGGATAATCATACTACTGCTTTACTACTCAACTGCTGCCTCCAGTTTGG  
CTGTAACATTGATGATAGCTATCTTTGTTGTTATATGGTCTCCAGAGACAATGTTTCTTGCTCC  
ATCTGTCTATAAGAGCTCTAAGTTAAAATGCTTCTTCGTCTCCTATTTATAATATGGTTTGTATT  
GTTAATTTTGTCTTGTAGAAGAGCTTAATTAATCGTTGTTGTTATGAAATACTATTTGTATGAGA  
TGAAGTGGTGAATGTAATTCATTTACATAAGTGGAGTCAGAATCAGAATGTTTCCCTCCATAACT  
AACTAGACATGAAGACCTGCCGCTACAATTGCTTATATTTGAACAATAAAATGAACATCTT  
TTGCCACAACCTTTATAAGTGGTTAATATAGCTCAAATATATGGTCAAGTTCATAGATTAATAAT  
GGAAATATCAGTTATCGAAATTCATTAACAATCAACTTAACGTTATTAATACTACTAATTTTATATCA  
TCCCCTTTGATAAATGATAGTACA

Fig. 64

SEQ ID NO: 73

HA from B/Florida/4/2006

AGAGGTACCCCGGGCTGGTATATTTATATGTTGTCAAATAACTCAAAAACCATAAAAAGTTTAAAGT  
TAGCAAGTGTGTACATTTTTACTTGAACAAAAATTCACCTACTACTGTTATAAATCATTATTAA  
ACATTAGAGTAAAGAAATATGGATGATAAGAACAAGAGTAGTGATATTTTGACAACAATTTTGT  
GCAACATTTGAGAAAATTTTGTGTTCTCTCTTTTCATTGGTCAAAAACAATAGAGAGAGAAAA  
GGAAGAGGGGAGAATAAAAACATAATGTGAGTATGAGAGAGAAAGTTGTACAAAAGTTGTACCAA  
AATAGTTGTACAAATATCATTGAGGAATTTGACAAAAGCTACACAAATAAGGGTTAATTGCTGTA  
AATAAATAAGGATGACGCATTAGAGAGATGTACCATTAGAGAATTTTTGGCAAGTCATTAATAAG  
AAAGAATAAATTATTTTTAAAATTAAGTTGAGTCATTTGATTAACATGTGATTATTTAATGAAT  
TGATGAAAGAGTTGGATTAAAGTTGTATTAGTAATTAGAATTTGGTGTCAAATTAATTTGACATT  
TGATCTTTTCTATATATTGCCCATAGAGTCAGTTAACTCATTTTTATATTTTCATAGATCAAATA  
AGAGAAATAACGGTATATTAATCCCTCCAAAAAACAACGGTATATTTACTAAAAATCTAAG  
CCACGTAGGAGGATAACAGGATCCCCGTAGGAGGATAACATCCAATCCAACCAATCACACAA  
TCCTGATGAGATAACCCACTTTAAGCCCACGCATCTGTGGCACATCTACATTATCTAAATCACA  
CATTCTCCACACATCTGAGCCACAAAAACAATCCACATCTTATCACCCATTCTATAAAAA  
ATCACACTTTGTGAGTCTACACTTTGATCCCTTCAAACACATACAAAAGAGAAGAGACTAATTA  
TTAATTAATCATCTTGAGAGAAAATGAAGGCAATAATTGTAATACTCATGGTAGTAACATCCAAT  
GCAGATCGAATCTGCACTGGAATAACATCTTCAAACCTCACCTCATGTGGTCAAACAGCCACTC  
AAGGGGAGGTCAATGTGACTGGTGTGATACCCTAACAAACACCAACAAAAATCTTATTTTGC  
AAATCTCAAAGGAACAAGGACCAGAGGGAAACTATGCCAGACTGTCTCAACTGCACAGATCT  
GGATGTGGCTTTGGGCAGACCAATGTGTGTGGGGACCACACCTTCGGCGAAGGCTTCAATAC  
TCCACGAAGTCAAACCTGTTACATCCGGGTGCTTTCTATAATGCACGACAGAACAATAATCAG  
GCAACTACCCAATCTTCTCAGAGGATATGAAAATATCAGGCTATCAACCCAAAACGTCATCGAT  
GCGGAAAAGGCACCAGGAGGCCCTACAGACTTGGAACTCAGGATCTTGCCCTAACGCTAC  
CAGTAAGAGCGGATTTTTCGCAACAATGGCTTGGGCTGTCCCAAAGGACAACAACAATAATGC  
AACGAACCCACTAACAGTAGAAGTACCATACATTTGTACAGAAGGGGAAGACCAATCACTGTT  
TGGGGGTTCCATTCAGATAACAAAACCCAAATGAAGAACCTCTATGGAGACTCAAATCCTCAA  
AGTTCACCTCATCTGCTAATGGAGTAACCACACACTATGTTTCTCAGATTGGCAGCTTCCGAG  
TCAAACAGAAGACGGAGGACTACCACAAAGCGGCAGGATTGTTGTTGATTACATGATGCAAAA  
ACCTGGGAAAAACAGGAACAATTGTCTACCAAAAGGTTGTTTTGTTGCCTCAAAGGTGTGGTG  
CGGAGTGGCAGGAGCAAAGTAATAAAAGGGTCTTGCCTTTAATTGGTGAAGCAGATTGCCCT  
TCATGAAAAATACGGTGGATTAAACAAAAGCAAGCCTTACTACACAGGAGAACATGCAAAAAGCC  
ATAGGAAATTGCCCAATATGGGTGAAAAACCTTTGAAGCTCGCCAATGGAACCAATATAGAC  
CTCCTGCAAAACTATTAAGGAAAGGGGTTTCTTCGGAGCTATTGCTGTTTTCTAGAAGGAG  
GATGGGAAGGAATGATTGCAGGCTGGCACGGATACACATCTCACGGAGCACATGGAGTGCCA  
GTGGCGGGCGGACCTTAAGAGTACGCAAGAAGCTATAAACAAGATAACAAAAAATCTCAATTCCT  
TGAGTGAGCTAGAAGTAAAGAATCTTCAAAGACTAAGTGGTGCCATGGATGAACTCCACAACG  
AAATACTCGAGCTGGATGAGAAAAGTGGATGATCTCAGAGCTGACACTATAAGCTCGCAAATG  
AACTTGCACTCTTGCTTTCCAACGAAGGAATAATAACAGTGAAGATGAGCATCTATTGGCACT  
TGAGAGAAAACATAAAGAAAATGCTGGGTCCCTCTGCTGTAGAGATAGGAAATGGATGCTTCGA  
AACCAACACAAGTGAACCCAGACCTGCTTAGACAGGATAGCTGCTGGCACCTTAAATGCAGG  
AGAATTTTCTCTCCCACTTTTGTACCTGAACATTAAGCTGCTGCATCTTAAATGATGATGGAT  
TGGATAACCATACTATACTGCTCTATTACTCAACTGCTGCTTCTAGTTTGGCTGTAACATTTGAT  
CTAGTATTTTTATTGTTTATATGGTCTCCAGAGACAAGTTTTATGCTCCATCTGTCTATAAGA  
GCTCTAAGTTAAAATGCTTCTCGTCTCTATTATAATATGGTTTGGTTATTGTTAATTTGTTCT  
TGTAGAAGAGCTTAATTAATCGTTGTTGTTATGAAATACTATTTGTATGAGATGAACTGGTGTA  
TGTAATTCATTTACATAAGTGGAGTCAGAATCAGAATGTTTCCATAACTAACTAGACATGAA  
GACCTGCCGCTACAATTGTCTTATATTTGAACAACATAAATGAACATCTTTGCCACAACCTT  
ATAAGTGGTTAATATAGCTCAAATATATGGTCAAGTTCAATAGATTAATAATGGAATATCAGTTA  
TCGAAATTCATTAACAATCAACTTAACGTTATTAATACTACTAATTTTATATCATCCCCTTTGATAAA  
TGATAGTACA

**Fig. 65**

Consensus of SEQ ID NO: 49, 48, 33 and 9

SEQ ID NO: 74

MK(X<sub>1</sub>)KLLVLLCTFTATYADTICIGYHANNSTDTVDTVLEKNVTVTHSVNLL  
E(X<sub>2</sub>)SHNGKLCLLKGIAPLQLGNCSVAGWILGNPECELLIS(X<sub>3</sub>)ESWSYIVE(X<sub>4</sub>)P  
NPENGTCTYPG(X<sub>5</sub>)FADYEELREQLSSVSSFERFEIFPKESSWPNHT(X<sub>6</sub>)TGVSA  
SCSHNG(X<sub>7</sub>)SSFY(X<sub>8</sub>)NLLWLTGKNGLYPNLSKSY(X<sub>9</sub>)NNKEKEVLVLWGVHPPN  
IG(X<sub>10</sub>)Q (X<sub>11</sub>)ALYH(X<sub>12</sub>)ENAYVSVSSHYSR(X<sub>13</sub>)FTPEIAKRPKVRDQEGRINYWTLL  
EPGDTIIFEANGNLIAP(X<sub>14</sub>)YAFALSRGFGSGII(X<sub>15</sub>)SNAPMD(X<sub>16</sub>)CDAKCQTPQG  
AINSSLPFQNVHPVTIGECPKYVRSKLRMVTGLRNIPSIQSRGLFGAIA  
GFIEGGWTGMVDGWYGYHHQNEQGSGYAADQKSTQNAINGITNKVNSVIE  
KMNTQFTAVGKEFNKLERRMENLNKKVDDGF(X<sub>17</sub>)DIWTYNAELLVLENERT  
LDFHDSNVKNLYEKVKSQKNNAKEIGNGCFEFYHKCN(X<sub>18</sub>)ECMESVKNQTY  
DYPKYSEESKLNREKIDGVKLESMGVYQILAIYSTVASSLVLLVSLGAIS  
FWMCSNGSLQCRICI

**Fig. 66**

SEQ ID NO: 75

MKAKLLVLLCTFTATYADTICIGYHANNSTDTVDTVLEKNVTVTHSVNLLLED SHNGKLCLLKGIA  
PLQLGNCSVAGWILGNPECELLISKESWSYIVETPNPENGTCPYGYFADYEELREQLSSVSSFERFEIF  
PKESSWPNHTVTGVSASC SHNGKSSFYRNLLWLTGKNGLYPNLSKSYVNNKEKEVLVLWGVHHPNI  
GNQRALYHTENAYVSVVSSHYSRRFTPEIAKRPKVRDQEGRINYWTLLEPGDTIIFEANGNLIAPWYAFALS  
RFGSGIITSNAPMDECDACQTPQGAINSSLPFQNVHPVTIGECPKYVRS AKLRMTGLRNIPSIQSRG  
LFGAIAGFIEGGWTGMVDGWYGYHHQNEQSGYAADQKSTQNAINGITNKVNSVIEKMNTQFTAVGK  
EFNKLERRMENLNKKVDDGFLDIWTYNAELLVLENERLDFHDSNVKNLYEKVKSQ LKNNAKEIGNGCFEF  
YHKCNNECMESVKNGTYDYPKYSEESKLNREKIDGVKLESMGVYQILAIYSTVASSLVLLVSLGAISFWMC  
SNGSLQCRICI

**Fig. 67**

SEQ ID NO: 76

MSLLTEVETYVLSIIPSGPLKAEIAQRLEDVFAGKNTDLEVLMEWLKTRPILSPLTKGILGFVFTLTGPS  
ERGLQRRRFVQNALNGNGDPNNMDKAVKLYRKLKREITFHGAKEISLSYSAGALASCMGLIYNRMGAV  
TTEVAFGLVCATCEQIADSQHRSHRQMVTTTNPLIRHENRMVLASTTAKAMEQMAGSSEQAAEAMEVAS  
QARQMVQAMRTIGTHPSSSAGLKNLLENLQAYQKRMGVQMQRFK

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**INFLUENZA VIRUS-LIKE PARTICLES  
(VLPS) COMPRISING HEMAGGLUTININ  
PRODUCED WITHIN A PLANT**

CROSS REFERENCE TO RELATED  
APPLICATIONS

This is a divisional application of U.S. application Ser. No. 12/669,033, filed Jun. 11, 2010, which was a national phase application of PCT/CA2008/001281, filed Jul. 11, 2008, which claims priority to U.S. Provisional Application No. 60/959,414, filed Jul. 13, 2007, U.S. Provisional Application No. 60/990,603, filed Nov. 27, 2007, U.S. Provisional Application No. 61/013,272, filed Dec. 12, 2007, U.S. Provisional Application No. 61/022,775, filed Jan. 22, 2008 and Canadian Application No. 2,615,372, filed Jan. 21, 2008, all of which are hereby incorporated by reference in the present disclosure in their entirety.

SUBMISSION OF SEQUENCE LISTING ON  
ASCII TEXT FILE

The content of the following submission on ASCII text file is incorporated herein by reference in its entirety: a computer readable form (CRF) of the Sequence Listing (file name: 267342000910SeqList.txt, date recorded: Jan. 3, 2013, size: 216 KB).

FIELD OF INVENTION

The present invention relates to the production of virus-like particles. More specifically, the present invention is directed to the production of virus-like particles comprising influenza antigens.

BACKGROUND OF THE INVENTION

Influenza is the leading cause of death in humans due to a respiratory virus. Common symptoms include fever, sore throat, shortness of breath, and muscle soreness, among others. During flu season, influenza viruses infect 10-20% of the population worldwide, leading to 250-500,000 deaths annually

Influenza viruses are enveloped virus that bud from the plasma membrane of infected mammalian cells. They are classified into types A, B, or C, based on the nucleoproteins and matrix protein antigens present. Influenza type A viruses may be further divided into subtypes according to the combination of hemagglutinin (HA) and neuraminidase (NA) surface glycoproteins presented. HA governs the ability of the virus to bind to and penetrate the host cell. NA removes terminal sialic acid residues from glycan chains on host cell and viral surface proteins, which prevents viral aggregation and facilitates virus mobility. Currently, 16 HA (H1-H16) and 9 NA (N1-N9) subtypes are recognized. Each type A influenza virus presents one type of HA and one type of NA glycoprotein. Generally, each subtype exhibits species specificity; for example, all HA and NA subtypes are known to infect birds, while only subtypes H1, H2, H3, H5, H7, H9, H10, N1, N2, N3 and N7 have been shown to infect humans (Horimoto 2006; Suzuki 2005). Influenza viruses comprising H5, H7 and H9 are considered the most highly pathogenic forms of influenza A viruses, and are most likely to cause future pandemics.

Influenza pandemics are usually caused by highly transmittable and virulent influenza viruses, and can lead to elevated levels of illness and death globally. The emergence

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of new influenza A subtypes resulted in 4 major pandemics in the 20<sup>th</sup> century. The Spanish flu, caused by an H1N1 virus, in 1918-1919 led to the deaths of over 50 million people worldwide between 1917 and 1920. Presently, the risk of the emergence of a new subtype, or of the transmission to humans of a subtype endemic in animals, is always present. Of particular concern is a highly virulent form of avian influenza (also called "bird flu"), outbreaks of which have been reported in several countries around the world. In many cases, this bird flu can result in mortality rates approaching 100% within 48 hours. The spread of the avian influenza virus (H5N1), first identified in Hong Kong in 1997, to other Asian countries and Europe has been postulated to be linked to the migratory patterns of wild birds.

The current method of combating influenza in humans is by annual vaccination. The vaccine is usually a combination of several strains that are predicted to be the dominant strains for the coming "flu-season". The prediction is coordinated by the World Health Organization. Generally, the number of vaccine doses produced each year is not sufficient to vaccinate the world's population. For example, Canada and the United-States obtain enough vaccines doses to immunize about one third of their population, while only 17% of the population of the European Union can be vaccinated. It is evident that current worldwide production of influenza vaccine would be insufficient in the face of a worldwide flu pandemic. Even if the necessary annual production could somehow be met in a given year, the dominant strains change from year to year, thus stockpiling at low-need times in the year is not practical. Economical, large scale production of an effective influenza vaccine is of significant interest to government and private industry alike.

The viral stocks for use in vaccines are produced in fertilized eggs. The virus particles are harvested, and for an inactivated viral vaccine, disrupted by detergent to inactivate. Live attenuated vaccines are made of influenza viruses that were adapted for growth at low temperature which means that at normal body temperature, the vaccine is attenuated. Such a vaccine is licensed in USA for use in individuals from 5 to 49 years of age. Inactivated whole virus vaccines are rendered harmless by inactivation with chemical agents and they have been produced in embryonic eggs or mammalian cell culture. All these types of vaccine show some specific advantages and disadvantages. One advantage of vaccines derived from whole viruses is the type of immunity induced by such vaccines. In general, split vaccines induce a strong antibody response while vaccines made of whole viruses induce both an antibody (humoral) and cellular response. Even though a functional antibody response is a criterion for licensure that correlates with protection induced by a vaccine, there is increasing evidence that a T-cell response is also important in influenza immunity—this may also provide better protection in the elderly.

In order to induce a cellular immune response, vaccines made of whole viruses were developed. Due to the high pathogenicity of the influenza strain (e.g. H5N1), these vaccines are produced in BL3+ facility. For highly pathogenic influenza strains such as H5N1, some manufacturers have modified the hemagglutinin gene sequence in order to reduce the pathogenicity of the influenza strain and to make it avirulent and more easily produced in embryonic eggs or mammalian cell culture. Others also use reassortant influenza strains in which the genetic sequences for the hemagglutinin and neuraminidase proteins are cloned in a high-yielding low pathogenic influenza donor strain (A/PR/8/34; Quan F-S et al, 2007). While these methods may produce useful vaccines, they do not provide a solution to the need

for high-volume, low cost and fast production of vaccines in the scale necessary to meet the global need in a normal year, and would almost certainly be insufficient in the face of a pandemic.

Using this reverse genetic technology, one might also need to mutate the genetic sequence of the HA protein to make it avirulent. For highly pathogenic influenza strains, the production of whole virus vaccines either requires confinement procedures or the resulting vaccines do not exactly match the genetic sequence of the circulating virus. In the case of live-attenuated vaccines, there is still a risk that the administered vaccine can recombine with an influenza virus from the host, leading to a new influenza virus.

While this method maintains the antigenic epitope and post-translational modifications, there are a number of drawbacks to this method, including the risk of contamination due to the use of whole virus and variable yields depending on virus strain. Sub-optimal levels of protection may result from genetic heterogeneity in the virus due to its introduction into eggs. Other disadvantages includes extensive planning for obtaining eggs, contamination risks due to chemicals used in purification, and long production times. Also, persons hypersensitive to egg proteins may not be eligible candidates for receiving the vaccine.

In the case of a pandemic, split vaccine production is limited by the need to adapt the strain for growth in eggs and the variable production yields achieved. Although this technology has been used for years for the production of seasonal vaccines, it can hardly respond in a reasonable timeframe to a pandemic and worldwide manufacturing capacity is limited.

To avoid the use of eggs, influenza viruses have also been produced in mammalian cell culture, for example in MDCK or PERC.6 cells, or the like. Another approach is reverse genetics, in which viruses are produced by cell transformation with viral genes. These methods, however, also requires the use of whole virus as well as elaborate methods and specific culture environments.

Several recombinant products have been developed as recombinant influenza vaccine candidates. These approaches have focused on the expression, production, and purification of influenza type A HA and NA proteins, including expression of these proteins using baculovirus infected insect cells (Crawford et al, 1999; Johansson, 1999), viral vectors, and DNA vaccine constructs (Olsen et al., 1997).

Specifics of an influenza virus infection are well known. Briefly, the infectious cycle is initiated by the attachment of the virion surface HA protein to a sialic acid-containing cellular receptor (glycoproteins and glycolipids). The NA protein mediates processing of the sialic acid receptor, and virus penetration into the cell depends on HA-dependent receptor-mediated endocytosis. In the acidic confines of internalized endosomes containing an influenza virion, the HA protein undergoes conformational changes that lead to fusion of viral and cell membranes and virus uncoating and M2-mediated release of M1 proteins from nucleocapsid-associated ribonucleoproteins (RNPs), which migrate into the cell nucleus for viral RNA synthesis. Antibodies to HA proteins prevent virus infection by neutralizing virus infectivity, whereas antibodies to NA proteins mediate their effect on the early steps of viral replication.

Crawford et al. (1999) disclose expression of influenza HA in baculovirus infected insect cells. The expressed proteins are described as being capable of preventing lethal influenza disease caused by avian H5 and H7 influenza subtypes. Johansson et al. (1999) teach that baculovirus-expressed influenza HA and NA proteins induce immune

responses in animals superior to those induced by a conventional vaccine. Immunogenicity and efficacy of baculovirus-expressed hemagglutinin of equine influenza virus was compared to a homologous DNA vaccine candidate (Olsen et al., 1997). Collectively, these data demonstrate that a high degree of protection against influenza virus challenge can be induced with recombinant HA or NA proteins, using various experimental approaches and in different animal models.

Since previous research has shown that the surface influenza glycoproteins, HA and NA, are the primary targets for elicitation of protective immunity against influenza virus and that M1 provides a conserved target for cellular immunity to influenza, a new vaccine candidate may include these viral antigens as a protein macromolecular particle, such as virus-like particles (VLPs). As vaccine products, VLPs offer the advantage of being more immunogenic than subunit or recombinant antigens and are able to stimulate both humoral and cellular immune response (Grgacic and Anderson, 2006). Further, the particle with these influenza antigens may display conformational epitopes that elicit neutralizing antibodies to multiple strains of influenza viruses.

Production of a non-infectious influenza virus strain for vaccine purposes is one way to avoid inadvertent infection. Alternatively, virus-like particles (VLPs) as substitutes for the cultured virus have been investigated. VLPs mimic the structure of the viral capsid, but lack a genome, and thus cannot replicate or provide a means for a secondary infection.

Several studies have demonstrated that recombinant influenza proteins self-assemble into VLPs in cell culture using mammalian expression plasmids or baculovirus vectors (Gomez-Puertas et al., 1999; Neumann et al., 2000; Latham and Galarza, 2001). Gomez-Puertas et al. (1999) discloses that efficient formation of influenza VLP depends on the expression levels of several viral proteins. Neumann et al. (2000) established a mammalian expression plasmid-based system for generating infectious influenza virus-like particles entirely from cloned cDNAs. Latham and Galarza (2001) reported the formation of influenza VLPs in insect cells infected with recombinant baculovirus co-expressing HA, NA, M1, and M2 genes. These studies demonstrated that influenza virion proteins may self-assemble upon co-expression in eukaryotic cells.

Gomez-Puertas et al. (2000) teach that, in addition to the hemagglutinin (HA), the matrix protein (M1) of the influenza virus is essential for VLP budding from insect cells. However, Chen et al. (2007) teach that M1 might not be required for VLP formation, and observed that efficient release of M1 and VLPs required the presence of HA and sialidase activity provided by NA. The NA cleaves the sialic acids of the glycoproteins at the surface of the cells producing the VLPs, and releasing the VLPs in the medium.

Quan et al 2007 teaches that a VLP vaccine produced in a baculovirus expression system (insect cell) induces a protective immunity against some strains of influenza virus (A/PR8/34 (H1N1)). The VLPs studied by Quan were observed to bud from the plasma membrane, and were considered to be of the correct size and morphology, similar to those obtained in a mammalian system (MDCK cells).

Enveloped viruses may obtain their lipid envelope when "budding" out of the infected cell and obtain the membrane from the plasma membrane, or from that of an internal organelle. Influenza virus particles and VLPs bud from the plasma membrane of the host cell. In mammalian or baculovirus cell systems, for example, influenza buds from the plasma membrane (Quan et al 2007). Only a few enveloped viruses are known to infect plants (for example, members of

the Topoviruses and Rhabdoviruses). Of the known plant enveloped viruses, they are characterized by budding from internal membranes of the host cell, and not from the plasma membrane. Although a small number of recombinant VLPs have been produced in plant hosts, none were derived from the plasma membrane, raising the question whether plasma membrane-derived VLPs, including influenza VLPs can be produced in plants.

Current influenza VLP production technologies rely on the co-expression of multiple viral proteins, and this dependence represents a drawback of these technologies since in case of a pandemic and of yearly epidemics, response time is crucial for vaccination. A simpler VLP production system, relying on the expression of only one viral protein is desirable to accelerate the development of vaccine.

In order to protect the world population from influenza and to stave off future pandemics, vaccine manufacturers will need to develop effective, rapid methods producing vaccine doses. The current use of fertilized eggs to produce vaccines is insufficient and involves a lengthy process.

#### SUMMARY OF THE INVENTION

It is an object of the invention to provide improved influenza virus like particles (VLPs).

According to the present invention there is provided a nucleic acid comprising a nucleotide sequence encoding an encoding an antigen from an enveloped virus operatively linked to a regulatory region active in a plant. The antigen may be an influenza hemagglutinin (HA).

The present invention also provides a method of producing influenza virus like particles (VLPs) in a plant comprising:

- a) introducing a nucleic acid encoding an antigen from an enveloped virus, for example an influenza hemagglutinin (HA), operatively linked to a regulatory region active in the plant, into the plant, or portion thereof, and
- b) incubating the plant or a portion thereof under conditions that permit the expression of the nucleic acid, thereby producing the VLPs.

The method may further comprise the steps of harvesting the plant and purifying or separating the VLPs from the plant tissue.

The present invention includes the above method wherein, in the step of introducing (step a), the nucleic acid may be either transiently expressed in the plant, or stably expressed in the plant. Furthermore, the VLPs may be purified using size exclusion chromatography.

The present invention also provides a virus like particle (VLP) comprising an influenza virus HA protein and one or more than one plant lipid.

Also included in the present invention is a composition comprising an effective dose of a VLP comprising an influenza virus HA protein, one or more than one plant lipid, and a pharmaceutically acceptable carrier.

The present invention also contemplates fragments or portions of HA proteins that form VLPs in a plant.

The VLP may comprise an HA protein of one, or more than one subtype, including H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15 or H16 or fragment or portion thereof. Examples of subtypes comprising such HA proteins include A/New Caledonia/20/99 (H1N1)/A/Indonesia/5/2006 (H5N1), A/chicken/New York/1995, A/herring gull/DE/677/88 (H2N8), A/Texas/32/2003, A/mallard/MN/33/00, A/duck/Shanghai/1/2000, A/northern pintail/TX/828189/02, A/Turkey/Ontario/6118/68(H8N4), A/shoveler/Iran/G54/03, A/chicken/Germany/N/1949

(H10N7), A/duck/England/56(H11N6), A/duck/Alberta/60/76(H12N5), A/Gull/Maryland/704/77(H13N6), A/Mallard/Gurjev/263/82, A/duck/Australia/341/83 (H15N8), A/black-headed gull/Sweden/5/99(H16N3), B/Lee/40, C/Johannesburg/66, A/PuertoRico/8/34 (H1N1), A/Brisbane/59/2007 (H1N1), A/Solomon Islands 3/2006 (H1N1), A/Brisbane 10/2007 (H3N2), A/Wisconsin/67/2005 (H3N2), B/Malaysia/2506/2004, B/Florida/4/2006, A/Singapore/1/57 (H2N2), A/Anhui/1/2005 (H5N1), A/Vietnam/1194/2004 (H5N1), A/Teal/HongKong/W312/97 (H6N1), A/Equine/Prague/56 (H7N7), A/HongKong/1073/99 (H9N2)).

In an aspect of the invention, the HA protein may be an H1, H2, H3, H5, H6, H7 or H9 subtype. In another aspect, the H1 protein may be from the A/New Caledonia/20/99 (H1N1), A/PuertoRico/8/34 (H1N1), A/Brisbane/59/2007 (H1N1), or A/Solomon Islands 3/2006 (H1N1) strain. The H3 protein may also be from the A/Brisbane 10/2007 (H3N2) or A/Wisconsin/67/2005 (H3N2) strain. In a further aspect of the invention, the H2 protein may be from the A/Singapore/1/57 (H2N2) strain. The H5 protein may be from the A/Anhui/1/2005 (H5N1), A/Vietnam/1194/2004 (H5N1), or A/Indonesia/5/2005 strain. In an aspect of the invention, the H6 protein may be from the A/Teal/HongKong/W312/97 (H6N1) strain. The H7 protein may be from the A/Equine/Prague/56 (H7N7) strain. In an aspect of the invention, the H9 protein is from the A/HongKong/1073/99 (H9N2) strain. In a further aspect of the invention, the HA protein may be from an influenza virus may be a type B virus, including B/Malaysia/2506/2004 or B/Florida/4/2006. Examples of amino acid sequences of the HA proteins from H1, H2, H3, H5, H6, H7 or H9 subtypes include SEQ ID NOs: 48-59.

The influenza virus HA protein may be H5 Indonesia.

The present invention also provides nucleic acid molecules comprising sequences encoding an HA protein. The nucleic acid molecules may further comprise one or more regulatory regions operatively linked to the sequence encoding an HA protein. The nucleic acid molecules may comprise a sequence encoding an H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15 or H16. In an aspect of the invention, the HA protein encoded by the nucleic acid molecule may be an H1, H2, H3, H5, H6, H7 or H9 subtype. The H1 protein encoded by the nucleic acid molecule is from the A/New Caledonia/20/99 (H1N1), A/PuertoRico/8/34 (H1N1), A/Brisbane/59/2007 (H1N1), or A/Solomon Islands 3/2006 (H1N1) strain. In an aspect of the invention, the H3 protein encoded by the nucleic acid molecule may be from the A/Brisbane 10/2007 (H3N2), or A/Wisconsin/67/2005 (H3N2) strain. In a further aspect of the invention, the H2 protein encoded by the nucleic acid molecule may be from the A/Singapore/1/57 (H2N2) strain. The H5 protein encoded by the nucleic acid molecule may also be from the A/Anhui/1/2005 (H5N1), A/Vietnam/1194/2004 (H5N1), or A/Indonesia/5/2005 strain. In an aspect of the invention, the H6 protein encoded by the nucleic acid molecule may be from the A/Teal/HongKong/W312/97 (H6N1) strain. The H7 protein encoded by the nucleic acid molecule may also be from the A/Equine/Prague/56 (H7N7) strain. Additionally, the H9 protein encoded by the nucleic acid molecule may be from the A/HongKong/1073/99 (H9N2) strain. Examples of sequences of nucleic acid molecules encoding such HA proteins from H1, H2, H3, H5, H6, H7 or H9 subtypes include SEQ ID NOs: 36-47 and 60-73.

The nucleic acid sequence may encode the influenza virus HA protein H5 Indonesia.

Regulatory regions that may be operatively linked to a sequence encoding an HA protein include those that are operative in a plant cell, an insect cell or a yeast cell. Such regulatory regions may include a plastocyanin regulatory region, a regulatory region of Ribulose 1,5-bisphosphate carboxylase/oxygenase (RuBisCO), chlorophyll a/b binding protein (CAB), ST-LS1, a polyhedrin regulatory region, or a gp64 regulatory region. Other regulatory regions include a 5' UTR, 3' UTR or terminator sequences. The plastocyanin regulatory region may be an alfalfa plastocyanin regulatory region; the 5' UTR, 3'UTR or terminator sequences may also be alfalfa sequences.

A method of inducing immunity to an influenza virus infection in a subject, is also provided, the method comprising administering the virus like particle comprising an influenza virus HA protein, one or more than one plant lipid, and a pharmaceutically acceptable carrier. The virus like particle may be administered to a subject orally, intradermally, intranasally, intramuscularly, intraperitoneally, intravenously, or subcutaneously.

The present invention also pertains to a virus like particle (VLP) comprising one or more than one protein derived from a virus selected from the group consisting of Influenza, Measles, Ebola, Marburg, and HIV, and one or more than one lipid derived from a non-sialylating host production cell. The HIV protein may be p24, gp120 or gp41; the Ebolavirus protein may be VP30 or VP35; the Marburg virus protein may be Gp/SGP; the Measles virus protein may be H-protein or F-protein.

Additionally the present invention relates to a virus like particle (VLP) comprising an influenza virus HA protein and one or more than one host lipid. For example if the host is insect, then the virus like particle (VLP) may comprise an influenza virus HA protein and one or more than one insect lipid, or if the host is a yeast, then the virus like particle (VLP) may comprise an influenza virus HA protein and one or more than one yeast lipid.

The present invention also relates to compositions comprising VLPs of two or more strains or subtypes of influenza. The two or more subtypes or strains may be selected from the group comprising: A/New Caledonia/20/99 (H1N1)/A/Indonesia/5/2006 (H5N1), A/chicken/New York/1995, A/herring gull/DE/677/88 (H2N8), A/Texas/32/2003, A/mallard/MN/33/00, A/duck/Shanghai/1/2000, A/northern pintail/TX/828189/02, A/Turkey/Ontario/6118/68(H8N4), A/shoveler/Iran/G54/03, A/chicken/Germany/N/1949 (H10N7), A/duck/England/56(H11N6), A/duck/Alberta/60/76(H12N5), A/Gull/Maryland/704/77(H13N6), A/Mallard/Gurjev/263/82, A/duck/Australia/341/83 (H15N8), A/black-headed gull/Sweden/5/99(H16N3), B/Lee/40, C/Johannesburg/66, A/PuertoRico/8/34 (H1N1), A/Brisbane/59/2007 (H1N1), A/Solomon Islands 3/2006 (H1N1), A/Brisbane 10/2007 (H3N2), A/Wisconsin/67/2005 (H3N2), B/Malaysia/2506/2004, B/Florida/4/2006, A/Singapore/1/57 (H2N2), A/Anhui/1/2005 (H5N1), A/Vietnam/1194/2004 (H5N1), A/Teal/HongKong/W312/97 (H6N1), A/Equine/Prague/56 (H7N7) or A/HongKong/1073/99 (H9N2)). The two or more subtypes or strains of VLPs may be present in about equivalent quantities; alternately one or more of the subtypes or strains may be the majority of the strains or subtypes represented.

The present invention pertains to a method for inducing immunity to influenza virus infection in an animal or target organism comprising administering an effective dose of a vaccine comprising one or more than one VLP, the VLP produced using a non-sialylating host, for example a plant host, an insect host, or a yeast host. The vaccine may be

administered orally, intradermally, intranasally, intramuscularly, intraperitoneally, intravenously, or subcutaneously. The target organism may be selected from the group comprising humans, primates, horses, pigs, birds (avian) water fowl, migratory birds, quail, duck, geese, poultry, chicken, camel, canine, dogs, feline, cats, tiger, leopard, civet, mink, stone marten, ferrets, house pets, livestock, mice, rats, seal, whales and the like.

The present invention provides a method for producing VLPs containing hemagglutinin (HA) from different influenza strains in a suitable host capable of producing a VLP, for example, a plant, insect, or yeast. VLPs that are produced in plants contain lipids of plant origin, VLPs produced in insect cells comprise lipids from the plasma membrane of insect cells (generally referred to as "insect lipids"), and VLPs produced in yeast comprise lipids from the plasma membrane of yeast cells (generally referred to as "yeast lipids").

The production of VLPs in plants presents several advantages over the production of these particles in insect cell culture. Plant lipids can stimulate specific immune cells and enhance the immune response induced. Plant membranes are made of lipids, phosphatidylcholine (PC) and phosphatidylethanolamine (PE), and also contain glycosphingolipids that are unique to plants and some bacteria and protozoa. Sphingolipids are unusual in that they are not esters of glycerol like PC or PE but rather consist of a long chain amino alcohol that forms an amide linkage to a fatty acid chain containing more than 18 carbons. PC and PE as well as glycosphingolipids can bind to CD1 molecules expressed by mammalian immune cells such as antigen-presenting cells (APCs) like dendritic cells and macrophages and other cells including B and T lymphocytes in the thymus and liver (Tsuji M., 2006). Furthermore, in addition to the potential adjuvant effect of the presence of plant lipids, the ability of plant N-glycans to facilitate the capture of glycoprotein antigens by antigen presenting cells (Saint-Jore-Dupas, 2007), may be advantageous of the production of VLPs in plants.

Without wishing to be bound by theory, it is anticipated that plant-made VLPs will induce a stronger immune reaction than VLPs made in other manufacturing systems and that the immune reaction induced by these plant-made VLPs will be stronger when compared to the immune reaction induced by live or attenuated whole virus vaccines.

Contrary to vaccines made of whole viruses, VLPs provide the advantage as they are non-infectious, thus restrictive biological containment is not as significant an issue as it would be working with a whole, infectious virus, and is not required for production. Plant-made VLPs provide a further advantage again by allowing the expression system to be grown in a greenhouse or field, thus being significantly more economical and suitable for scale-up.

Additionally, plants do not comprise the enzymes involved in synthesizing and adding sialic acid residues to proteins. VLPs may be produced in the absence of neuraminidase (NA), and there is no need to co-express NA, or to treat the producing cells or extract with sialidase (neuraminidase), to ensure VLP production in plants.

The VLPs produced in accordance with the present invention do not comprise M1 protein which is known to bind RNA. RNA is a contaminant of the VLP preparation and is undesired when obtaining regulatory approval for the VLP product.

This summary of the invention does not necessarily describe all features of the invention.

#### BRIEF DESCRIPTION OF THE DRAWINGS

These and other features of the invention will become more apparent from the following description in which reference is made to the appended drawings wherein:

FIG. 1A shows a sequence of an alfalfa plastocyanin-based expression cassette used for the expression of H1 in accordance with an embodiment of the present invention (SEQ ID NO:8). Protein disulfide isomerase (PDI) signal peptide is underlined. BglIII (AGATCT) and SacI (GAGCTC) restriction sites used for cloning are shown in bold. FIG. 1B shows a schematic diagram of functional domains of influenza hemagglutinin. After cleavage of HA0, HA1 and HA2 fragments remain bound together by a disulfide bridge.

FIG. 2A shows a representation of plasmid 540 assembled for the expression of HA subtype H1. FIG. 2B shows a representation of plasmid 660 assembled for the expression of HA subtype H5.

FIG. 3A shows the elution profile from a size exclusion chromatography of protein extracts from leaves producing hemagglutinin H1; Blue Dextran 2000 (triangles) and proteins (diamonds). FIG. 3B shows immunodetection (western blot; anti H1) of H1 elution fractions following size exclusion chromatography (S500HR beads). FIG. 3C show the elution profile of H5; Blue Dextran 2000 (triangles) and proteins (diamonds). FIG. 3D shows immunodetection (western blot; anti H5) of H5 elution fractions following size exclusion chromatography (S500HR beads).

FIG. 4A shows an electron microscopy photomicrograph of large hemagglutinin H1 structures from elution fraction 9 from a size exclusion column showing a 50 000-fold enlargement of a VLP from H1 showing the presence of multiple similar structures (the bar represents 200 nm). FIG. 4B shows a 150 000-fold enlargement of a VLP from H1 (the bar represents 100 nm). FIG. 4C shows a 50 000-fold enlargement of a VLP from H5 showing the presence of multiple similar structures (the bar represents 50 nm).

FIG. 5A shows the sequence of the N terminal fragment of H1 (SEQ ID NO:1). FIG. 5B shows the C terminal fragment of H1 (SEQ ID NO:2). FIG. 5C shows the complete sequence encoding HA0 of H1 (SEQ ID NO:28).

FIG. 6 shows the sequence encoding H5 flanked by a HindIII site immediately upstream of the initial ATG, and a SacI site immediately downstream of the stop (TAA) codon (SEQ ID NO:3).

FIG. 7A shows the sequence of the primer Plasto-443c (SEQ ID NO:4). FIG. 7B shows the sequence of primer SpHA(Ind)-Plasto.r (SEQ ID NO:5). FIG. 7C shows the sequence of primer Plasto-SpHA(Ind).c (SEQ ID NO:6). FIG. 7D shows the sequence of primer HA(Ind)-Sac.r (SEQ ID NO:7).

FIG. 8A shows the amino acid sequence of the HA1 peptide sequence (SEQ ID NO:9). FIG. 8B shows the amino acid sequence of HAS peptide sequence (SEQ ID NO:10). Native signal peptide is indicated in bold.

FIG. 9 shows the sequence of HA of influenza A subtype H7 (SEQ ID No: 11).

FIG. 10A shows the sequence of Influenza A HA, subtype H2 (SEQ ID NO:12). FIG. 10B shows the sequence of Influenza A HA subtype H3 (SEQ ID NO:13). FIG. 10C shows the sequence of Influenza A HA subtype H4 (SEQ ID NO:14). FIG. 10D shows the sequence of Influenza A HA subtype H5 (SEQ ID NO:15). FIG. 10E shows the sequence

of Influenza A HA subtype H6 (SEQ ID NO:16). FIG. 10F shows the sequence of Influenza A HA subtype H8 (SEQ ID NO:17). FIG. 10G shows the sequence of Influenza A HA subtype H9 (SEQ ID NO:18). FIG. 10H shows the sequence of Influenza A HA subtype H10 (SEQ ID NO:19). FIG. 10I shows the sequence of Influenza A HA subtype H11 (SEQ ID NO:20). FIG. 10J shows the sequence of Influenza A HA subtype H12 (SEQ ID NO:21). FIG. 10K shows the sequence of Influenza A HA subtype H13 (SEQ ID NO:22). FIG. 10L shows the sequence of Influenza A HA subtype H14 (SEQ ID NO:23). FIG. 10M shows the sequence of Influenza A HA subtype H15 (SEQ ID NO:24). FIG. 10N shows the sequence of Influenza A HA subtype H16 (SEQ ID NO:25). FIG. 10O shows the sequence of Influenza B HA (SEQ ID NO:26). FIG. 10P shows the sequence of Influenza C HA (SEQ ID NO:27). FIG. 10Q shows the sequence of primer XmaI-pPlas.c (SEQ ID NO: 29). FIG. 10R shows the sequence of primer SacI-ATG-pPlas.r (SEQ ID NO: 30). FIG. 10S shows the sequence of primer SacI-PlasTer.c (SEQ ID NO: 31). FIG. 10T shows the sequence of primer EcoRI-PlasTer.r (SEQ ID NO: 32).

FIG. 11 shows a schematic representation of several constructs as used herein. Construct 660 comprises the nucleotide sequence to encode the HA subtype H5 under operatively linked to the plastocyanin promoter (plasto) and terminator (Pter); construct 540 comprises the nucleotide sequence to encode the HA subtype H1 in combination with an alfalfa protein disulfide isomerase signal peptide (SP PDI), and is operatively linked to a plastocyanin promoter (Plasto) and terminator (Pter); construct 544 assembled for the expression of HA subtype H1, the nucleotide sequence encoding H1 is combined with an alfalfa protein disulfide isomerase signal peptide (SP PDI) and an GCN4pII leucine zipper (in place of the transmembrane domain and cytoplasmic tail of HI) and operatively linked to the plastocyanin promoter (Plasto) and terminator (Pter); and construct 750 for the expression of M1 coding region from influenza A/PR/8/34 is combined to the tobacco etch virus (TEV) 5'UTR, and operatively linked with the double 35S promoter and Nos terminator.

FIG. 12 shows immunodetection of H5, using anti-H5 (Vietnam) antibodies, in protein extracts from *N. benthamiana* leaves transformed with construct 660 (lane 3). Commercial H5 from influenza A/Vietnam/1203/2004 was used as positive control of detection (lane 1), and a protein extract from leaves transformed with an empty vector were used as negative control (lane 2).

FIG. 13A shows characterization of hemagglutinin structures by size exclusion chromatography. Protein extract from separate biomasses producing H5, H1, soluble H1, or H1 and M1 were separated by gel filtration on S-500 HR. Commercial H1 in the form of rosettes was also fractionated (H1 rosette). Elution fractions were analyzed for relative protein content (Relative Protein Level—a standard protein elution profile of a biomass fractionation is shown). Blue Dextran 2000 (2 MDa reference standard) elution peak is indicated. FIG. 13B shows elution fractions analyzed for the presence of hemagglutinin by immunoblotting with anti-H5 (Vietnam) antibodies (for H5). FIG. 13C shows elution fractions analyzed for anti-influenza A antibodies for H1. FIG. 13D shows elution fractions analyzed for anti-influenza A antibodies for soluble H1. FIG. 13E shows elution fractions analyzed for anti-influenza A antibodies for H1 rosette. FIG. 13F shows elution fractions analyzed for anti-influenza A antibodies for H1+M1.

FIG. 14A shows concentration of influenza H5 structures by sucrose gradient centrifugation and electron microscopy

examination of hemagglutinin-concentrated fractions and characterization of fractions from sucrose density gradient centrifugation. Each fraction was analyzed for the presence of H5 by immunoblotting using anti-H5 (Vietnam) antibodies (upper panel), and for their relative protein content and hemagglutination capacity (graph). FIG. 14B shows negative staining transmission electron microscopy examination of pooled fractions 17, 18 and 19 from sucrose gradient centrifugation. The bar represents 100 nm.

FIG. 15A shows purification of influenza H5 VLPs; Coomassie Blue stained SDS-PAGE analysis of protein content in the clarification steps—lane 1, crude extract; lane 2, pH 6-adjusted extract; lane 3, heat-treated extract; lane 4, DE-filtrated extract; the fetuin affinity purification steps: lane 5, load; lane 6, wash; lane 7, elution (10× concentrated). FIG. 15B shows negative staining transmission electron microscopy examination of the purified H5 VLP sample. The bar represents 100 nm. FIG. 15 C shows isolated H5 VLP enlarged to show details of the structure. FIG. 15D shows the H5 VLP product on a Coomassie-stained reducing SDS-PAGE (lane A) and Western blot (lane B) using rabbit polyclonal antibody raised against HA from strain A/Vietnam/1203/2004 (H5N1).

FIG. 16 shows a nucleotide sequence for Influenza A virus (A/New Caledonia/20/99(H1N1)) hemagglutinin (HA) gene, complete cds. GenBank Accession No. AY289929 (SEQ ID NO: 33).

FIG. 17 shows a nucleotide sequence for *Medicago sativa* mRNA for protein disulfide isomerase. GenBank Accession No. Z11499 (SEQ ID NO: 34).

FIG. 18 shows a nucleotide sequence for Influenza A virus (A/Puerto Rico/8/34(H1N1)) segment 7, complete sequence. GenBank Accession No. NC\_002016.1 (SEQ ID NO: 35).

FIG. 19 shows localization of VLP accumulation by positive staining transmission electron microscopy observation of H5 producing tissue. CW: cell wall, ch: chloroplast, pm: plasma membrane, VLP: virus-like particle. The bar represents 100 nm.

FIG. 20(A) Induction of serum antibody responses 14 days after boost in Balb/c mice vaccinated with plant-made influenza H5 VLP or recombinant soluble HA through intramuscular injection. FIG. 20(B) Antibody responses of mice immunized through intranasal administration. Antibody responses were measured against inactivated whole H5N1 viruses (A/Indonesia/5/05). GMT: geometric mean titer. Values are the GMT (log<sub>2</sub>) of reciprocal end-point titers of five mice per group. Bars represent mean deviation. \* p<0.05 compared to recombinant soluble HA.

FIG. 21(A) Hemagglutination inhibition antibody response (HAI) 14 days after boost in Balb/c mice vaccinated with plant-made influenza H5 VLP or recombinant soluble HA through intramuscular injection. FIG. 21(B) Antibody responses of mice immunized through intranasal administration. HAI antibody responses were measured using inactivated whole H5N1 viruses (A/Indonesia/5/05). GMT: geometric mean titer. Values are the GMT (log<sub>2</sub>) of reciprocal end-point titers of five mice per group. Bars represent mean deviation. \* p<0.05 and \*\* p<0.01 compared to recombinant soluble HA.

FIG. 22(A) Effect of alum on immunogenicity of the VLPs in mice immunized through intramuscular injection. FIG. 22(B) Effect of Chitosan on immunogenicity of the VLPs in mice immunized through intranasal administration. HAI antibody responses were measured using inactivated whole H5N1 viruses (A/Indonesia/5/05). GMT: geometric mean titer. Values are the GMT (log<sub>2</sub>) of reciprocal end-

point titers of five mice per group. Bars represent mean deviation. \*p<0.05 compared to the corresponding recombinant soluble HA.

FIG. 23(A) Antibody response to VLP administration using Anti-Indonesia/5/05 immunoglobulin isotype in mice vaccinated with intramuscular injection, 30 days after boost. Values are the GMT (log<sub>2</sub>) of reciprocal end-point titers of five mice per group. ELISA performed using whole inactivated viruses as the coating agent. Bars represent mean deviation. \* p<0.05, \*\* p<0.001 compared to the corresponding recombinant soluble HA. FIG. 23(B) Antibody titers against whole inactivated viruses. All groups are statistically different to negative control.

FIG. 24 shows antibody titer against homologous whole inactivated viruses (A/Indonesia/5/05), 2 weeks after first dose (week 2), 14 days after boost (week 5) or 30 days after boost (week 7). GMT: geometric mean titer. Values are the GMT (log<sub>2</sub>) of reciprocal end-point titers of five mice per group. \* p<0.05 compared to recombinant soluble HA.

FIG. 25(A) Antibody titers against whole inactivated viruses show in vitro cross-reactivity of serum. FIG. 25(B) Hemagglutination-inhibition titers against various whole inactivated viruses. Values are the GMT (log<sub>2</sub>) of reciprocal end-point titers of five mice per group. Bars represent mean deviation. All groups are statistically different to negative control. \* p<0.05, \*\* p<0.001 compared to the corresponding recombinant soluble HA.

FIG. 26(A) Survival rate of mice after challenge with 10 LD<sub>50</sub> (4.09×10<sup>5</sup> CCID<sub>50</sub>) of plant made VLP H5, influenza strain A/Turkey/582/06 (H5N1). FIG. 26(B) Body weight of immunised mice after challenge. Values are the mean body weight of surviving mice.

FIG. 27 (A) Polar lipid composition of purified influenza VLPs. Lipids contained in an equivalent of 40 µg of proteins, were extracted from VLP as described, separated by HP-TLC, and compared to the migration profile of lipids isolated from highly purified tobacco plasma membrane (PM). Lipid abbreviations are as following: DGDG, Digalactosyldiacylglycerol; gluCER, glucosyl-ceramide; PA, phosphatic acid; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PG, phosphatidylglycerol; PI, phosphatidylinositol; PS, phosphatidylserine; SG, Steryl-glycoside. FIG. 27(B) Neutral lipid composition of purified influenza VLPs. Lipids contained in an equivalent of 20 µg of proteins were extracted from VLP as described, separated by HP-TLC and compared to the migration of sitosterol. FIG. 27(C) Immunodetection of the plasma membrane marker proton pump ATPase (PMA) in purified VLPs and highly-purified PM from tobacco leaves (PML) and BY2 tobacco cells (PMBY2). Eighteen micrograms of protein were loaded in each lane.

FIG. 28 shows the sequence spanning from DraIII to SacI sites of clone 774-nucleotide sequence of A/Brisbane/59/2007 (H1N1) (SEQ ID NO: 36). The coding sequence is flanked by a plastocyanin regulatory region, starting with a DraIII restriction site at the 5' end and by a stop codon and a SacI site at the 3' end. Restriction sites are underlined; ATG is in bold and underlined.

FIG. 29 shows the sequence spanning from DraIII to SacI sites of clone 775-nucleotide sequence of A/Solomon Islands 3/2006 (H1N1) (SEQ ID NO: 37). The coding sequence is flanked by a plastocyanin regulatory region, starting with a DraIII restriction site at the 5' end and by a stop codon and a SacI site at the 3' end. Restriction sites are underlined; ATG is in bold and underlined.

FIG. 30 shows the sequence spanning from DraIII to SacI sites of clone 776-nucleotide sequence of A/Brisbane

10/2007 (H1N1) (SEQ ID NO: 38). The coding sequence is flanked by a plastocyanin regulatory region, starting with a DraIII restriction site at the 5' end and by a stop codon and a SacI site at the 3' end. Restriction sites are underlined; ATG is in bold and underlined.

FIG. 31 shows the sequence spanning from DraIII to SacI sites of clone 777-nucleotide sequence of A/Wisconsin/67/2005 (H3N2) (SEQ ID NO: 39). The coding sequence is flanked by a plastocyanin regulatory region, starting with a DraIII restriction site at the 5' end and by a stop codon and a SacI site at the 3' end. Restriction sites are underlined; ATG is in bold and underlined.

FIG. 32 shows the sequence spanning from DraIII to SacI sites of clone 778-nucleotide sequence of B/Malaysia/2506/2004 (SEQ ID NO: 40). The coding sequence is flanked by a plastocyanin regulatory region, starting with a DraIII restriction site at the 5' end and by a stop codon and a SacI site at the 3' end. Restriction sites are underlined; ATG is in bold and underlined.

FIG. 33 shows the sequence spanning from DraIII to SacI sites of clone 779-nucleotide sequence of B/Florida/4/2006 (SEQ ID NO: 41). The coding sequence is flanked by a plastocyanin regulatory region, starting with a DraIII restriction site at the 5' end and by a stop codon and a SacI site at the 3' end. Restriction sites are underlined; ATG is in bold and underlined.

FIG. 34 shows the sequence spanning from DraIII to SacI sites of clone 780-nucleotide sequence of A/Singapore/1/57 (H2N2) (SEQ ID NO: 42). The coding sequence is flanked by a plastocyanin regulatory region, starting with a DraIII restriction site at the 5' end and by a stop codon and a SacI site at the 3' end. Restriction sites are underlined; ATG is in bold and underlined.

FIG. 35 shows the sequence spanning from DraIII to SacI sites of clone 781-nucleotide sequence of A/Anhui/1/2005 (H5N1) (SEQ ID NO: 43). The coding sequence is flanked by a plastocyanin regulatory region, starting with a DraIII restriction site at the 5' end and by a stop codon and a SacI site at the 3' end. Restriction sites are underlined; ATG is in bold and underlined.

FIG. 36 shows the sequence spanning from DraIII to SacI sites of clone 782-nucleotide sequence of A/Vietnam/1194/2004 (H5N1) (SEQ ID NO: 44). The coding sequence is flanked by a plastocyanin regulatory region, starting with a DraIII restriction site at the 5' end and by a stop codon and a SacI site at the 3' end. Restriction sites are underlined; ATG is in bold and underlined.

FIG. 37 shows the sequence spanning from DraIII to SacI sites of clone 783-nucleotide sequence of A/Teal/HongKong/W312/97 (H6N1) (SEQ ID NO: 45). The coding sequence is flanked by a plastocyanin regulatory region, starting with a DraIII restriction site at the 5' end and by a stop codon and a SacI site at the 3' end. Restriction sites are underlined; ATG is in bold and underlined.

FIG. 38 shows the sequence spanning from DraIII to SacI sites of clone 784-nucleotide sequence of A/Equine/Prague/56 (H7N7) (SEQ ID NO: 46). The coding sequence is flanked by a plastocyanin regulatory region, starting with a DraIII restriction site at the 5' end and by a stop codon and a SacI site at the 3' end. Restriction sites are underlined; ATG is in bold and underlined.

FIG. 39 shows the sequence spanning from DraIII to SacI sites of clone 785-nucleotide sequence of A/HongKong/1073/99 (H9N2) (SEQ ID NO: 47). The coding sequence is flanked by a plastocyanin regulatory region, starting with a

DraIII restriction site at the 5' end and by a stop codon and a SacI site at the 3' end. Restriction sites are underlined; ATG is in bold and underlined.

FIG. 40A shows the amino acid sequence (SEQ ID NO: 48) of the polypeptide translated from clone 774 (A/Brisbane/59/2007 (H1N1)). The open reading frame of clone 774 starts with the ATG indicated in FIG. 28. FIG. 40B shows the amino acid sequence (SEQ ID NO: 49) of the polypeptide translated from clone 775 (A/Solomon Islands 3/2006 (H1N1)). The open reading frame of clone 775 starts with the ATG indicated in FIG. 29.

FIG. 41A shows the amino acid sequence (SEQ ID NO: 50) of the polypeptide translated from clone 776 (A/Brisbane/10/2007 (H3N2)). The open reading frame of clone 776 starts with the ATG indicated in FIG. 30. FIG. 41B shows the amino acid sequence (SEQ ID NO: 51) of the polypeptide translated from clone 777 (A/Wisconsin/67/2005 (H3N2)). The open reading frame of clone 777 starts with the ATG indicated in FIG. 31.

FIG. 42A shows the amino acid sequence (SEQ ID NO: 52) of the polypeptide translated from clone 778 (B/Malaysia/2506/2004). The open reading frame of clone 778 starts with the ATG indicated in FIG. 32. FIG. 42B shows the amino acid sequence (SEQ ID NO: 53) of the polypeptide translated from clone 779 (B/Florida/4/2006). The open reading frame of clone 779 starts with the ATG indicated in FIG. 33.

FIG. 43A shows the amino acid sequence (SEQ ID NO: 54) of the polypeptide translated from clone 780 (A/Singapore/1/57 (H2N2)). The open reading frame of clone 780 starts with the ATG indicated in FIG. 34. FIG. 43B shows the amino acid sequence (SEQ ID NO: 55) of the polypeptide translated from clone 781 (A/Anhui/1/2005 (H5N1)). The open reading frame of clone 781 starts with the ATG indicated in FIG. 35.

FIG. 44A shows the amino acid sequence (SEQ ID NO: 56) of the polypeptide translated from clone 782 (A/Vietnam/1194/2004 (H5N1)). The open reading frame of clone 782 starts with the ATG indicated in FIG. 36. FIG. 44B shows the amino acid sequence (SEQ ID NO: 57) of the polypeptide translated from clone 783 (A/Teal/HongKong/W312/97 (H6N1)). The open reading frame of clone 783 starts with the ATG indicated in FIG. 37.

FIG. 45A shows the amino acid sequence (SEQ ID NO: 58) of the polypeptide translated from clone 784 (A/Equine/Prague/56 (H7N7)). The open reading frame of clone 784 starts with the ATG indicated in FIG. 38. FIG. 45B shows the amino acid sequence (SEQ ID NO: 59) of the polypeptide translated from clone 785 (A/HongKong/1073/99 (H9N2)). The open reading frame of clone 785 starts with the ATG indicated in FIG. 39.

FIG. 46 shows immunodetection (western blot) of elution fractions of plant-produced VLPs, following size exclusion chromatography. Hemagglutinin subtypes H1, H2, H5, H6 and H9 are shown. Hemagglutinin is detected in fractions 7-14, corresponding to the elution of VLPs.

FIG. 47 shows an immunoblot analysis of expression of a series of H1 hemagglutinin from annual epidemic strains. Ten and twenty micrograms of protein extracts were loaded in lanes 1 and 2, respectively.

FIG. 48 shows an immunoblot analysis of expression of a series of H5 hemagglutinin from potential pandemic strains. Ten and twenty micrograms of protein extracts were loaded in lanes 1 and 2, respectively.

FIG. 49 show an immunoblot of H5 from strain A/Indonesia/5/2005 in protein extracts from *Nicotiana tabacum* leaves, agroinfiltrated with AGL1/660. Two plants were

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infiltrated and 10 and 20  $\mu$ g of soluble protein from each plant were loaded in lanes 1 and 2, respectively.

FIG. 50(A) Hemagglutination-inhibition (HI) titers in ferret sera, 14 days after 1st immunization and FIG. 50(B) after 2nd boost with plant-made influenza H5 VLP show the in vitro cross-reactivity of serum antibodies. HAI antibody responses were measured using the following inactivated whole H5N1 viruses: A/turkey/Turkey/1/05, A/Vietnam/1194/04, A/Anhui/5/05 and the homologous strain A/Indonesia/5/05. Values are the GMT (log 2) of reciprocal endpoint titers of five ferrets per group. Diagonal stripe—A/Indonesia/6/06 (clade 2.1.3); checked—A/turkey/Turkey/1/05 (clade 2.2); white bar—A/Vietnam/1194/04 (clade 1); black bar A/Anhui/5/05. Responders are indicated. Bars represent mean deviation.

FIG. 51 shows the nucleic acid sequence of an HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H5 from A/Indonesia/5/2005 (Construct #660), alfalfa plastocyanin 3' UTR and terminator sequences.

FIG. 52 shows the nucleic acid sequence of an HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H1 from A/New Caledonia/20/1999 (Construct #540), alfalfa plastocyanin 3' UTR and terminator sequences.

FIG. 53 shows the nucleic acid sequence of an HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H1 from A/Brisbane/59/2007 (construct #774), alfalfa plastocyanin 3' UTR and terminator sequences.

FIG. 54 shows the nucleic acid sequence of an HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H1 from A/Solomon Islands/3/2006 (H1N1) (construct #775), alfalfa plastocyanin 3' UTR and terminator sequences.

FIG. 55 shows the nucleic acid sequence of an HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H2 from A/Singapore/1/57 (H2N2) (construct #780), alfalfa plastocyanin 3' UTR and terminator sequences.

FIG. 56 shows the nucleic acid sequence of an HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H5 from A/Anhui/1/2005 (H5N1) (Construct #781), alfalfa plastocyanin 3' UTR and terminator sequences.

FIG. 57 shows the nucleic acid sequence of an HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H5 from A/Vietnam/1194/2004 (H5N1) (Construct #782), alfalfa plastocyanin 3' UTR and terminator sequences.

FIG. 58 shows the nucleic acid sequence of an HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H6 from A/Teal/Hong Kong/W312/97 (H6N1) (Construct #783), alfalfa plastocyanin 3' UTR and terminator sequences.

FIG. 59 shows the nucleic acid sequence of an HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H9 from A/Hong Kong/1073/99 (H9N2) (Construct #785), alfalfa plastocyanin 3' UTR and terminator sequences.

FIG. 60 shows the nucleic acid sequence of an HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H3 from A/Brisbane/10/2007 (H3N2), alfalfa plastocyanin 3' UTR and terminator sequences.

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FIG. 61 shows the nucleic acid sequence of an HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H3 from A/Wisconsin/67/2005 (H3N2), alfalfa plastocyanin 3' UTR and terminator sequences.

FIG. 62 shows the nucleic acid sequence of an HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H7 from A/Equine/Prague/56 (H7N7), alfalfa plastocyanin 3' UTR and terminator sequences.

FIG. 63 shows the nucleic acid sequence of an HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of HA from B/Malaysia/2506/2004, alfalfa plastocyanin 3' UTR and terminator sequences.

FIG. 64 shows the nucleic acid sequence of an HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of HA from B/Florida/4/2006, alfalfa plastocyanin 3' UTR and terminator sequences.

FIG. 65 shows a consensus amino acid sequence (SEQ ID NO: 74) for HA of A/New Caledonia/20/99 (H1N1) (encoded by SEQ ID NO: 33), A/Brisbane/59/2007 (H1N1) (SEQ ID NO: 48), A/Solomon Islands/3/2006 (H1N1) (SEQ ID NO: 49) and SEQ ID NO: 9. X1 (position 3) is A or V; X2 (position 52) is D or N; X3 (position 90) is K or R; X4 (position 99) is K or T; X5 (position 111) is Y or H; X6 (position 145) is V or T; X7 (position 154) is E or K; X8 (position 161) is R or K; X9 (position 181) is V or A; X10 (position 203) is D or N; X11 (position 205) is R or K; X12 (position 210) is T or K; X13 (position 225) is R or K; X14 (position 268) is W or R; X15 (position 283) is T or N; X16 (position 290) is E or K; X17 (position 432) is I or L; X18 (position 489) is N or D.

FIG. 66 shows Amino acid sequence of H1 New Caledonia (AAP34324.1) encoded by SEQ ID NO: 33.

FIG. 67 shows the Amino acid sequence of H1 Puerto Rico (NC\_0409878.1) encoded by SEQ ID NO: 35.

#### DETAILED DESCRIPTION

The present invention relates to the production of virus-like particles. More specifically, the present invention is directed to the production of virus-like particles comprising influenza antigens. The following description is of a preferred embodiment.

The present invention provides a nucleic acid comprising a nucleotide sequence encoding an antigen from an enveloped virus, for example, the influenza hemagglutinin (HA), operatively linked to a regulatory region active in a plant.

Furthermore, the present invention provides a method of producing virus like particles (VLPs) in a plant. The method involves introducing a nucleic acid encoding an antigen operatively linked to a regulatory region active in the plant, into the plant, or portion of the plant, and incubating the plant or a portion of the plant under conditions that permit the expression of the nucleic acid, thereby producing the VLPs.

VLPs may be produced from influenza virus, however, VLPs may also be produced from other plasma membrane derived virus including but not limited to Measles, Ebola, Marburg, and HIV.

The invention includes VLPs of all types of influenza virus which may infect humans, including for example, but not limited to the very prevalent A (H1N1) sub-type (e.g. A/New Caledonia/20/99 (H1N1)), the A/Indonesia/5/05 sub-type (H5N1) (SEQ ID NO: 60) and the less common B

type (for example SEQ ID NO:26, FIG. 10O), and C type (SEQ ID NO:27, FIG. 10P), and to HAs obtained from other influenza subtypes. VLPs of other influenza subtypes are also included in the present invention, for example, A/Brisbane/59/2007 (H1N1; SEQ ID NO:48), A/Solomon Islands/3/2006 (H1N1; SEQ ID NO:49), A/Singapore/1/57 (H2N2; SEQ ID NO:54), A/Anhui/1/2005 (H5N1; SEQ ID NO:55), A/Vietnam/1194/2004 (H5N1; SEQ ID NO:56), A/Teal/Hong Kong/W312/97 (H6N1; SEQ ID NO:57), A/Hong Kong/1073/99 (H9N2; SEQ ID NO:59), A/Brisbane/10/2007 (H3N2; SEQ ID NO:50), A/Wisconsin/67/2005 (H3N2; SEQ ID NO:51), A/Equine/Prague/56 (H7N7; SEQ ID NO:58), B/Malaysia/2506/2004 (SEQ ID NO:52), or B/Florida/4/2006 (SEQ ID NO:53).

The present invention also pertains to influenza viruses which infect other mammals or host animals, for example humans, primates, horses, pigs, birds, avian water fowl, migratory birds, quail, duck, geese, poultry, chicken, camel, canine, dogs, feline, cats, tiger, leopard, civet, mink, stone marten, ferrets, house pets, livestock, mice, rats, seal, whale and the like.

Non limiting examples of other antigens that may be expressed in plasma membrane derived viruses include, the Capsid protein of HIV-p24; gp120, gp41-envelope proteins, the structural proteins VP30 and VP35; Gp/SGP (a glycosylated integral membrane protein) of Filoviruses, for example Ebola or Marburg, or the H protein, and F protein of Paramyxoviruses, for example, Measles.

The invention also includes, but is not limited to, influenza derived VLPs that obtain a lipid envelope from the plasma membrane of the cell in which the VLP proteins are expressed. For example, if the VLP is expressed in a plant-based system, the VLP may obtain a lipid envelope from the plasma membrane of the cell.

Generally, the term “lipid” refers to a fat-soluble (lipophilic), naturally-occurring molecules. The term is also used more specifically to refer to fatty-acids and their derivatives (including tri-, di-, and monoglycerides and phospholipids), as well as other fat-soluble sterol-containing metabolites or sterols. Phospholipids are a major component of all biological membranes, along with glycolipids, sterols and proteins. Examples of phospholipids include phosphatidylethanolamine, phosphatidylcholine, phosphatidylinositol, phosphatidylserine, and the like. Examples of sterols include zoosterols (e.g., cholesterol) and phytosterols. Over 200 phytosterols have been identified in various plant species, the most common being campesterol, stigmasterol, ergosterol, brassicasterol, delta-7-stigmasterol, delta-7-avenasterol, daunossterol, sitosterol, 24-methylcholesterol, cholesterol or beta-sitosterol. As one of skill in the art would understand, the lipid composition of the plasma membrane of a cell may vary with the culture or growth conditions of the cell or organism from which the cell is obtained.

Cell membranes generally comprise lipid bilayers, as well as proteins for various functions. Localized concentrations of particular lipids may be found in the lipid bilayer, referred to as ‘lipid rafts’. Without wishing to be bound by theory, lipid rafts may have significant roles in endo and exocytosis, entry or egress of viruses or other infectious agents, inter-cell signal transduction, interaction with other structural components of the cell or organism, such as intracellular and extracellular matrices.

With reference to influenza virus, the term “hemagglutinin” or “HA” as used herein refers to a glycoprotein found on the outside of influenza viral particles. HA is a homotrimeric membrane type I glycoprotein, generally comprising a signal peptide, an HA1 domain, and an HA2 domain

comprising a membrane-spanning anchor site at the C-terminus and a small cytoplasmic tail (FIG. 1B). Nucleotide sequences encoding HA are well known and are available—see, for example, the BioDefence Public Health base or National Center for Biotechnology Information, both of which are incorporated herein by reference.

The term “homotrimer” or “homotrimeric” indicates that an oligomer is formed by three HA protein molecules. Without wishing to be bound by theory, HA protein is synthesized as monomeric precursor protein (HA0) of about 75 kDa, which assembles at the surface into an elongated trimeric protein. Before trimerization occurs, the precursor protein is cleaved at a conserved activation cleavage site (also referred to as fusion peptide) into 2 polypeptide chains, HA1 and HA2 (comprising the transmembrane region), linked by a disulfide bond. The HA1 segment may be 328 amino acids in length, and the HA2 segment may be 221 amino acids in length. Although this cleavage may be important for virus infectivity, it may not be essential for the trimerization of the protein. Insertion of HA within the endoplasmic reticulum (ER) membrane of the host cell, signal peptide cleavage and protein glycosylation are co-translational events. Correct refolding of HA requires glycosylation of the protein and formation of 6 intra-chain disulfide bonds. The HA trimer assembles within the cis- and trans-Golgi complex, the transmembrane domain playing a role in the trimerization process. The crystal structures of bromelain-treated HA proteins, which lack the transmembrane domain, have shown a highly conserved structure amongst influenza strains. It has also been established that HA undergoes major conformational changes during the infection process, which requires the precursor HA0 to be cleaved into the 2 polypeptide chains HA1 and HA2. The HA protein may be processed (i.e., comprise HA1 and HA2 domains), or may be unprocessed (i.e. comprise the HA0 domain).

The present invention pertains to the use of an HA protein comprising the transmembrane domain and includes HA1 and HA2 domains, for example the HA protein may be HA0, or processed HA comprising HA1 and HA2. The HA protein may be used in the production or formation of VLPs using a plant, or plant cell, expression system.

The HA of the present invention may be obtained from any subtype. For example, the HA may be of subtype H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, or H16. The recombinant HA of the present invention may also comprise an amino acid sequence based on the sequence any hemagglutinin known in the art—see, for example, the BioDefence Public Health base or National Center for Biotechnology Information. Furthermore, the HA may be based on the sequence of a hemagglutinin that is isolated from one or more emerging or newly-identified influenza viruses.

The present invention also includes VLPs that comprise HAs obtained from one or more than one influenza subtype. For example, VLPs may comprise one or more than one HA from the subtype H1 (encoded by SEQ ID NO:28), H2 (encoded by SEQ ID NO:12), H3 (encoded by SEQ ID NO:13), H4 (encoded by SEQ ID NO:14), H5 (encoded by SEQ ID NO:15), H6 (encoded by SEQ ID NO:16), H7 (encoded by SEQ ID NO:11), H8 (encoded by SEQ ID NO:17), H9 (encoded by SEQ ID NO:18), H10 (encoded by SEQ ID NO:19), H11 (encoded by SEQ ID NO:20), H12 (encoded by SEQ ID NO:21), H13 (encoded by SEQ ID NO:27), H14 (encoded by SEQ ID NO:23), H15 (encoded by SEQ ID NO:24), H16 (encoded by SEQ ID NO:25), or a combination thereof. One or more than one HA from the

one or more than one influenza subtypes may be co-expressed within a plant or insect cell to ensure that the synthesis of the one or more than one HA results in the formation of VLPs comprising a combination of HAs obtained from one or more than one influenza subtype. Selection of the combination of HAs may be determined by the intended use of the vaccine prepared from the VLP. For example a vaccine for use in inoculating birds may comprise any combination of HA subtypes, while VLPs useful for inoculating humans may comprise subtypes one or more than one of subtypes H1, H2, H3, H5, H7, H9, H10, N1, N2, N3 and N7. However, other HA subtype combinations may be prepared depending upon the use of the inoculum.

Therefore, the present invention is directed to a VLP comprising one or more than one HA subtype.

The present invention also provides for nucleic acids encoding hemagglutinins that form VLPs when expressed in plants

Influenza HA proteins exhibit a range of similarities and differences with respect to molecular weight, isoelectric point, size, glycan complement and the like. The physico-chemical properties of the various hemagglutinins may be useful to allow for differentiation between the HAs expressed in a plant, insect cell or yeast system, and may be of particular use when more than one HA is co-expressed in a single system. Examples of such physico-chemical properties are provided in Table 1.

Hybridization under stringent hybridization conditions is known in the art (see for example Current Protocols in Molecular Biology, Ausubel et al., eds. 1995 and supplements; Maniatis et al., in Molecular Cloning (A Laboratory Manual), Cold Spring Harbor Laboratory, 1982; Sambrook and Russell, in Molecular Cloning: A Laboratory Manual, 3<sup>rd</sup> edition 2001; each of which is incorporated herein by reference). An example of one such stringent hybridization conditions may be about 16-20 hours hybridization in 4×SSC at 65° C., followed by washing in 0.1×SSC at 65° C. for an hour, or 2 washes in 0.1×SSC at 65° C. each for 20 or 30 minutes. Alternatively, an exemplary stringent hybridization condition could be overnight (16-20 hours) in 50% formamide, 4×SSC at 42° C., followed by washing in 0.1×SSC at 65° C. for an hour, or 2 washes in 0.1×SSC at 65° C. each for 20 or 30 minutes, or overnight (16-20 hours), or hybridization in Church aqueous phosphate buffer (7% SDS; 0.5M NaPO<sub>4</sub> buffer pH 7.2; 10 mM EDTA) at 65° C., with 2 washes either at 50° C. in 0.1×SSC, 0.1% SDS for 20 or 30 minutes each, or 2 washes at 65° C. in 2×SSC, 0.1% SDS for 20 or 30 minutes each.

Additionally, the present invention includes nucleotide sequences that are characterized as having about 70, 75, 80, 85, 87, 90, 91, 92, 93 94, 95, 96, 97, 98, 99, 100% or any amount therebetween, sequence identity, or sequence similarity, with the nucleotide sequence encoding HA from H1 (SEQ ID NO:28), H5 (SEQ ID NO:3) or H7 (SEQ ID

TABLE 1

			Physico-chemical properties of influenza hemagglutinins														
Clone			AA			Glycans			Molecular Weight (kDa)						Isoelectric point		
No	Type	Influenza strains	HA0	HA1	HA2	HA0	HA1	HA2	HA0	HA0 <sup>1</sup>	HA1	HA1 <sup>1</sup>	HA2	HA2 <sup>1</sup>	HA0	HA1	HA2
774	H1	A/Brisbane/59/2007	548	326	222	9	7	2	61	75	36	47	25	28	6.4	7.5	5.3
775	H1	A/Solomon Islands/3/2006	548	326	222	9	7	2	61	75	36	47	25	28	6.1	6.7	5.3
776	H3	A/Brisbane/10/2007	550	329	221	12	11	1	62	80	37	54	25	27	8.5	9.6	5.2
777	H3	A/Wisconsin/67/2005	550	329	221	11	10	1	62	79	37	52	25	27	8.8	9.6	5.3
778	B	B/Malaysia/2506/2004	570	347	223	12	8	4	62	80	38	50	24	30	8.0	9.7	4.5
779	B	B/Florida/4/2006	569	346	223	10	7	3	62	77	38	48	24	29	8.0	9.7	4.5
780	H2	A/Singapore/1/57	547	325	222	6	4	2	62	71	36	42	25	28	6.0	7.5	4.9
781	H5	A/Anhui/1/2005	551	329	222	7	5	2	62	73	37	45	25	28	6.2	8.9	4.7
782	H5	A/Vietnam/1194/2004	552	330	222	7	5	2	63	74	38	45	25	28	6.4	9.1	4.8
783	H6	A/Teal/Hong Kong/W312/97	550	328	222	8	5	3	62	75	37	45	25	30	5.7	5.9	5.6
784	H7	A/Equine/Prague/56	552	331	221	6	4	2	62	71	37	43	25	28	8.9	9.7	4.9
785	H9	A/Hong Kong/1073/99	542	320	199	9	7	2	61	75	36	46	23	26	8.4	9.5	5.3

The present invention also includes nucleotide sequences SEQ ID NO:28; SEQ ID NO:3; SEQ ID NO:11, encoding HA from H1, H5 or H7, respectively, a nucleotide sequence that hybridizes under stringent hybridisation conditions to SEQ ID NO:28; SEQ ID NO:3; SEQ ID NO:11, or a nucleotide sequence that hybridizes under stringent hybridisation conditions to a complement of SEQ ID NO:28; SEQ ID NO:3; SEQ ID NO:1, wherein the nucleotide sequence encodes a hemagglutinin protein that when expressed forms a VLP, and that the VLP induces the production of an antibody when administered to a subject. For example, expression of the nucleotide sequence within a plant cell forms a VLP, and the VLP may be used to produce an antibody that is capable of binding HA, including mature HA, HA0, HA1, or HA2 of one or more influenza types or subtypes. The VLP, when administered to a subject, induces an immune response.

NO:11), wherein the nucleotide sequence encodes a hemagglutinin protein that when expressed forms a VLP, and that the VLP induces the production of an antibody. For example, expression of the nucleotide sequence within a plant cell forms a VLP, and the VLP may be used to produce an antibody that is capable of binding HA, including mature HA, HA0, HA1, or HA2. The VLP, when administered to a subject, induces an immune response.

Similarly, the present invention includes HAs associated with the following subtypes H1 (encoded by SEQ ID NO:28), H2 (encoded by SEQ ID NO:12), H3 (encoded by SEQ ID NO:13), H4 (encoded by SEQ ID NO:14), H5 (encoded by SEQ ID NO:15), H6 (encoded by SEQ ID NO:16), H7 (encoded by SEQ ID NO:11), H8 (encoded by SEQ ID NO:17), H9 (encoded by SEQ ID NO:18), H10 (encoded by SEQ ID NO:19), H11 (encoded by SEQ ID NO:20), H12 (encoded by SEQ ID NO:21), H13 (encoded

by SEQ ID NO:27), H14 (encoded by SEQ ID NO:23), H15 (encoded by SEQ ID NO:24), H16 (encoded by SEQ ID NO:25); see FIGS. 10A to 10P), and nucleotide sequences that are characterized as having from about 70 to 100% or any amount therebetween, 80 to 100% or any amount therebetween, 90-100% or any amount therebetween, or 95-100% or any amount therebetween, sequence identity with H1 (SEQ ID NO:28), H2 (SEQ ID NO:12), H3 (SEQ ID NO:13), H4 (SEQ ID NO:14), H5 (SEQ ID NO:15), H6 (SEQ ID NO:16), H7 (SEQ ID NO:11), H8 (SEQ ID NO:17), H9 (SEQ ID NO:18), H10 (SEQ ID NO:19), H11 (SEQ ID NO:20), H12 (SEQ ID NO:21), H13 (SEQ ID NO:27), H14 (SEQ ID NO:23), H15 (SEQ ID NO:24), H16 (SEQ ID NO:25), wherein the nucleotide sequence encodes a hemagglutinin protein that when expressed forms a VLP, and that the VLP induces the production of an antibody. For example, expression of the nucleotide sequence within a plant cell forms a VLP, and the VLP may be used to produce an antibody that is capable of binding HA, including mature HA, HA0, HA1, or HA2. The VLP, when administered to a subject, induces an immune response.

An "immune response" generally refers to a response of the adaptive immune system. The adaptive immune system generally comprises a humoral response, and a cell-mediated response. The humoral response is the aspect of immunity that is mediated by secreted antibodies, produced in the cells of the B lymphocyte lineage (B cell). Secreted antibodies bind to antigens on the surfaces of invading microbes (such as viruses or bacteria), which flags them for destruction. Humoral immunity is used generally to refer to antibody production and the processes that accompany it, as well as the effector functions of antibodies, including Th2 cell activation and cytokine production, memory cell generation, opsonin promotion of phagocytosis, pathogen elimination and the like. The terms "modulate" or "modulation" or the like refer to an increase or decrease in a particular response or parameter, as determined by any of several assays generally known or used, some of which are exemplified herein.

A cell-mediated response is an immune response that does not involve antibodies but rather involves the activation of macrophages, natural killer cells (NK), antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen. Cell-mediated immunity is used generally to refer to some Th cell activation, Tc cell activation and T-cell mediated responses. Cell mediated immunity is of particular importance in responding to viral infections.

For example, the induction of antigen specific CD8 positive T lymphocytes may be measured using an ELISPOT assay; stimulation of CD4 positive T-lymphocytes may be measured using a proliferation assay. Anti-influenza antibody titres may be quantified using an ELISA assay; isotypes of antigen-specific or cross reactive antibodies may also be measured using anti-isotype antibodies (e.g. anti-IgG, IgA, IgE or IgM). Methods and techniques for performing such assays are well-known in the art.

A hemagglutination inhibition (HI, or HAI) assay may also be used to demonstrate the efficacy of antibodies induced by a vaccine, or vaccine composition can inhibit the agglutination of red blood cells (RBC) by recombinant HA. Hemagglutination inhibitory antibody titers of serum samples may be evaluated by microtiter HAI (Aymard et al 1973). Erythrocytes from any of several species may be used—e.g. horse, turkey, chicken or the like. This assay

gives indirect information on assembly of the HA trimer on the surface of VLP, confirming the proper presentation of antigenic sites on HAs.

Cross-reactivity HAI titres may also be used to demonstrate the efficacy of an immune response to other strains of virus related to the vaccine subtype. For example, serum from a subject immunized with a vaccine composition of a first strain (e.g. VLPs of A/Indonesia 5/05) may be used in an HAI assay with a second strain of whole virus or virus particles (e.g. A/Vietnam/1194/2004), and the HAI titer determined.

Cytokine presence or levels may also be quantified. For example a T-helper cell response (Th1/Th2) will be characterized by the measurement of IFN- $\gamma$  and IL-4 secreting cells using by ELISA (e.g. BD Biosciences OptEIA kits). Peripheral blood mononuclear cells (PBMC) or splenocytes obtained from a subject may be cultured, and the supernatant analyzed. T lymphocytes may also be quantified by fluorescence-activated cell sorting (FACS), using marker specific fluorescent labels and methods as are known in the art.

A microneutralization assay may also be conducted to characterize an immune response in a subject, see for example the methods of Rowe et al., 1973. Virus neutralization titers may be obtained several ways, including: 1) enumeration of lysis plaques (plaque assay) following crystal violet fixation/coloration of cells; 2) microscopic observation of cell lysis in culture; 3) ELISA and spectrophotometric detection of NP virus protein (correlate with virus infection of host cells)

Sequence identity or sequence similarity may be determined using a nucleotide sequence comparison program, such as that provided within DNASIS (for example, using, but not limited to, the following parameters: GAP penalty 5, # of top diagonals 5, fixed GAP penalty 10, k-tuple 2, floating gap 10, and window size 5). However, other methods of alignment of sequences for comparison are well-known in the art for example the algorithms of Smith & Waterman (1981, Adv. Appl. Math. 2:482), Needleman & Wunsch (J. Mol. Biol. 48:443, 1970), Pearson & Lipman (1988, Proc. Nat'l. Acad. Sci. USA 85:2444), and by computerized implementations of these algorithms (e.g. GAP, BESTFIT, FASTA, and BLAST), or by manual alignment and visual inspection.

The term "hemagglutinin domain" refers to a peptide comprising either the HA0 domain, or the HA1 and HA2 domains. The hemagglutinin domain does not include the signal peptide, transmembrane domain, or the cytoplasmic tail found in the naturally occurring protein.

The term "virus like particle" (VLP), or "virus-like particles" or "VLPs" refers to structures that self-assemble and comprise structural proteins such as influenza HA protein. VLPs are generally morphologically and antigenically similar to virions produced in an infection, but lack genetic information sufficient to replicate and thus are non-infectious. In some examples, VLPs may comprise a single protein species, or more than one protein species. For VLPs comprising more than one protein species, the protein species may be from the same species of virus, or may comprise a protein from a different species, genus, subfamily or family of virus (as designated by the ICTV nomenclature). In other examples, one or more of the protein species comprising a VLP may be modified from the naturally occurring sequence. VLPs may be produced in suitable host cells including plant and insect host cells. Following extraction from the host cell and upon isolation and further purification under suitable conditions, VLPs may be purified as intact structures.

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The VLPs produced from influenza derived proteins, in accordance with the present invention do not comprise M1 protein. The M1 protein is known to bind RNA (Wakefield and Brownlee, 1989) which is a contaminant of the VLP preparation. The presence of RNA is undesired when obtaining regulatory approval for the VLP product, therefore a VLP preparation lacking RNA may be advantageous.

The VLPs of the present invention may be produced in a host cell that is characterized by lacking the ability to sialylate proteins, for example lacking sialidase, such as a plant cell, an insect cell, fungi, and other organisms including sponge, coelenterata, annelida, arthropoda, mollusca, nemathelminthes, trochelmintes, plathelminthes, chaetognatha, tentaculate, *chlamydia*, spirochetes, gram-positive bacteria, cyanobacteria, archaeobacteria, as identified in glycoforum. The VLPs produced as described herein do not typically comprise neuraminidase (NA). However, NA may be co-expressed with HA should VLPs comprising HA and NA be desired.

A VLP produced in a plant according to some aspects of the invention may be complexed with plant-derived lipids. The VLP may comprise an HA0, HA1 or HA2 peptide. The plant-derived lipids may be in the form of a lipid bilayer, and may further comprise an envelope surrounding the VLP. The plant derived lipids may comprise lipid components of the plasma membrane of the plant where the VLP is produced, including, but not limited to, phosphatidylcholine (PC), phosphatidylethanolamine (PE), glycosphingolipids, phytosterols or a combination thereof. A plant-derived lipid may alternately be referred to as a 'plant lipid'. Examples of phytosterols are known in the art, and include, for example, stigmasterol, sitosterol, 24-methylcholesterol and cholesterol—see, for example, Mongrand et al., 2004.

VLPs may be assessed for structure and size by, for example, hemagglutination assay, electron microscopy, or by size exclusion chromatography.

For size exclusion chromatography, total soluble proteins may be extracted from plant tissue by homogenizing (Polytron) sample of frozen-crushed plant material in extraction buffer, and insoluble material removed by centrifugation. Precipitation with PEG may also be of benefit. The soluble protein is quantified, and the extract passed through a Sephacryl™ column. Blue Dextran 2000 may be used as a calibration standard. Following chromatography, fractions may be further analyzed by immunoblot to determine the protein complement of the fraction.

Without wishing to be bound by theory, the capacity of HA to bind to RBC from different animals is driven by the affinity of HA for sialic acids  $\alpha$ 2,3 or  $\alpha$ 2,3 and the presence of these sialic acids on the surface of RBC. Equine and avian HA from influenza viruses agglutinate erythrocytes from all several species, including turkeys, chickens, ducks, guinea pigs, humans, sheep, horses and cows; whereas human HAs will bind to erythrocytes of turkey, chickens, ducks, guinea pigs, humans and sheep (see also Ito T. et al, 1997, Virology, vol 227, p493-499; and Medeiros R et al, 2001, Virology, vol 289 p. 74-85). Examples of the species reactivity of HAs of different influenza strains is shown in Tables 2A and 2B.

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TABLE 2A

Species of RBC bound by HAs of selected seasonal influenza strains.						
Seasonal	Strain	No	Origin	Horse	Turkey	
5	H1	A/Brisbane/59/2007 (H1N1)	774	Human	+	++
		A/Solomon Islands/3/2006 (H1N1)	775	Human	+	++
10	H3	A/Brisbane/10/2007 (H3N2)	776	Human	+	++
		A/Wisconsin/67/2005 (H3N2)	777	Human	+	++
15	B	B/Malaysia/2506/2004	778	Human	+	++
		B/Florida/4/2006	779	Human	+	++

TABLE 2B

Species of RBC bound by HAs of selected pandemic influenza strains						
Pandemic	Strain	No	Origine	Horse	Turkey	
20	H2	A/Singapore/1/57 (H2N2)	780	Human	+	++
	H5	A/Anhui/1/2005 (H5N1)	781	Hu-Av	++	+
25		A/Vietnam/1194/2004 (H5N1)	782	Hu-Av	++	+
	H6	A/Teal/Hong Kong/W312/97 (H6N1)	783	Avian	++	+
30	H7	A/Equine/Prague/56 (H7N7)	784	Equine	++	++
	H9	A/Hong Kong/1073/99 (H9N2)	785	Human	++	+

As used herein, a "protein" refers generally to a string of amino acids connected by a peptide bond, which may be folded into secondary, tertiary or quaternary structure to achieve a particular morphology. Alternately, the terms polypeptide, peptide or peptide fragments may be used in a similar context.

A fragment or portion of a protein, fusion protein or polypeptide includes a peptide or polypeptide comprising a subset of the amino acid complement of a particular protein or polypeptide, provided that the fragment can form a VLP when expressed. The fragment may, for example, comprise an antigenic region, a stress-response-inducing region, or a region comprising a functional domain of the protein or polypeptide. The fragment may also comprise a region or domain common to proteins of the same general family, or the fragment may include sufficient amino acid sequence to specifically identify the full-length protein from which it is derived.

For example, a fragment or portion may comprise from about 60% to about 100%, of the length of the full length of the protein, or any amount therebetween, provided that the fragment can form a VLP when expressed. For example, from about 60% to about 100%, from about 70% to about 100%, from about 80% to about 100%, from about 90% to about 100%, from about 95% to about 100%, of the length of the full length of the protein, or any amount therebetween. Alternately, a fragment or portion may be from about 150 to about 500 amino acids, or any amount therebetween, depending upon the HA, and provided that the fragment can form a VLP when expressed. For example, a fragment may be from 150 to about 500 amino acids, or any amount therebetween, from about 200 to about 500 amino acids, or any amount therebetween, from about 250 to about 500 amino acids, or any amount therebetween, from about 300 to about 500 or any amount therebetween, from about 350 to about 500 amino acids, or any amount therebetween, from

about 400 to about 500 or any amount therebetween, from about 450 to about 500 or any amount therebetween, depending upon the HA, and provided that the fragment can form a VLP when expressed. For example, about 5, 10, 20, 30, 40 or 50 amino acids, or any amount therebetween may be removed from the C terminus, the N terminus or both the N and C terminus of an HA protein, provided that the fragment can form a VLP when expressed.

Numbering of amino acids in any given sequence are relative to the particular sequence, however one of skill can readily determine the 'equivalency' of a particular amino acid in a sequence based on structure and/or sequence. For example, if 6 N terminal amino acids were removed when constructing a clone for crystallography, this would change the specific numerical identity of the amino acid (e.g. relative to the full length of the protein), but would not alter the relative position of the amino acid in the structure.

Comparisons of a sequence or sequences may be done using a BLAST algorithm (Altschul et al., 1990. *J. Mol Biol* 215:403-410). A BLAST search allows for comparison of a query sequence with a specific sequence or group of sequences, or with a larger library or database (e.g. GenBank or GenPept) of sequences, and identify not only sequences that exhibit 100% identity, but also those with lesser degrees of identity. Nucleic acid or amino acid sequences may be compared using a BLAST algorithm. Furthermore the identity between two or more sequences may be determined by aligning the sequences together and determining the % identity between the sequences. Alignment may be carried out using the BLAST Algorithm (for example as available through GenBank; using default parameters: Program: blastn; Database: nr; Expect 10; filter: default; Alignment: pairwise; Query genetic Codes: Standard(1)), or BLAST2 through EMBL using default parameters: Matrix BLO-SUM62; Filter: default, echofilter: on, Expect:10, cutoff: default; Strand: both; Descriptions: 50, Alignments: 50; or FASTA, using default parameters), or by manually comparing the sequences and calculating the % identity.

The present invention describes, but is not limited to, the cloning of a nucleic acid encoding HA into a plant expression vector, and the production of influenza VLPs from the plant, suitable for vaccine production. Examples of such nucleic acids include, for example, but are not limited to, an influenza A/New Caledonia/20/99 (H1N1) virus HA (e.g. SEQ ID NO: 61), an HA from A/Indonesia/5/05 sub-type (H5N1) (e.g. SEQ ID NO: 60), A/Brisbane/59/2007 (H1N1) (e.g. SEQ ID NO: 36, 48, 62), A/Solomon Islands/3/2006 (H1N1) (e.g. SEQ ID NO: 37, 49, 63), A/Singapore/1/57 (H2N2) (e.g. SEQ ID NO: 42, 54, 64), A/Anhui/1/2005 (H5N1) (e.g. SEQ ID NO: 43, 55, 65), A/Vietnam/1194/2004 (H5N1) (e.g. SEQ ID NO: 44, 56, 66), A/Teal/Hong Kong/W312/97 (H6N1) (e.g. SEQ ID NO: 45, 57, 67), A/Hong Kong/1073/99 (H9N2) (e.g. SEQ ID NO: 47, 59, 68), A/Brisbane/10/2007 (H3N2) (e.g. SEQ ID NO: 38, 50, 69), A/Wisconsin/67/2005 (H3N2) (e.g. SEQ ID NO: 39, 51, 70), A/Equine/Prague/56 (H7N7) (e.g. SEQ ID NO: 46, 58, 71), B/Malaysia/2506/2004 (e.g. SEQ ID NO: 40, 52, 72), B/Florida/4/2006 (e.g. SEQ ID NO: 41, 53, 73). The corresponding clone or construct numbers for these strains is provided in Table 1. Nucleic acid sequences corresponding to SEQ ID NOs: 36-47 comprise a plastocyanin upstream and operatively linked to the coding sequence of the HA for each of the types or subtypes, as illustrated in FIGS. 28-39. Nucleic acid sequences corresponding to SEQ ID NO: 60-73 comprise an HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding

sequence of an HA, alfalfa plastocyanin 3' UTR and terminator sequences, as illustrated in FIGS. 51-64.

The VLPs may also be used to produce reagents comprised of recombinant influenza structural proteins that self-assemble into functional and immunogenic homotypic macromolecular protein structures, including subviral influenza particles and influenza VLP, in transformed hosts cells, for example plant cells or insect cells.

Therefore, the invention provides for VLPs, and a method for producing viral VLPs in a plant expression system, from the expression of a single envelope protein. The VLPs may be influenza VLPs, or VLPs produced from other plasma membrane-derived virus including, but not limited to, Measles, Ebola, Marburg, and HIV.

Proteins from other enveloped viruses, for example but not limited to Filoviridae (e.g. Ebola virus, Marburg virus, or the like), Paramyxoviridae (e.g. Measles virus, Mumps virus, Respiratory syncytial virus, pneumoviruses, or the like), Retroviridae (e.g. Human Immunodeficiency Virus-1, Human Immunodeficiency Virus-2, Human T-Cell Leukemia Virus-1, or the like), Flaviviridae (e.g. West Nile Encephalitis, Dengue virus, Hepatitis C virus, yellow fever virus, or the like), Bunyaviridae (e.g. Hantavirus or the like), Coronaviridae (e.g. coronavirus, SARS, or the like), as would be known to those of skill in the art, may also be used. Non limiting examples of antigens that may be expressed in plasma membrane derived viruses include, the capsid protein of HIV-p24; HIV glycoproteins gp120 or gp41, Filovirus proteins including VP30 or VP35 of Ebolavirus or Gp/SGP of Marburg virus or the H protein or F protein of the Measles paramyxovirus. For example, P24 of HIV (e.g. GenBank reference gi:19172948) is the protein obtained by translation and cleavage of the gag sequence of the HIV virus genome (e.g. GenBank reference gi:9629357); gp120 and gp41 of HIV are glycoproteins obtained by translation and cleavage of the gp160 protein (e.g. GenBank reference gi:9629363), encoded by env of the HIV virus genome. VP30 of Ebolavirus (GenPept Reference gi: 55770813) is the protein obtained by translation of the vp30 sequence of the Ebolavirus genome (e.g. GenBank Reference gi:55770807); VP35 of Ebolavirus (GenPept Reference gi:55770809) is the protein obtained by translation of the vp35 sequence of the Ebolavirus genome. Gp/SGP of Marburg virus (GenPept Reference gi:296965) is the protein obtained by translation of the (sequence) of the Marburg virus genome (GenBank Reference gi:158539108). H protein (GenPept Reference gi: 9626951) is the protein of the H sequence of the Measles virus genome (GenBank Reference gi: 9626945); F protein (GenPept reference gi: 9626950) is the protein of the F sequence of the Measles virus genome.

However, other coat proteins may be used within the methods of the present invention as would be known to one of skill in the art.

The invention, therefore, provides for a nucleic acid molecule comprising a sequence encoding HIV-p24, HIV-gp120, HIV-gp41, Ebolavirus-VP30, Ebolavirus-VP35, Marburg virus Gp/SGP, Measles virus-H protein or -F protein. The nucleic acid molecule may be operatively linked to a regulatory region active in an insect, yeast or plant cell, or in a particular plant tissue.

The present invention further provides the cloning of a nucleic acid encoding an HA, for example but not limited to, human influenza A/Indonesia/5/05 virus HA (H5N1) into a plant or insect expression vector (e.g. baculovirus expression vector) and production of influenza vaccine candidates or reagents comprised of recombinant influenza structural proteins that self-assemble into functional and immunogenic

homotypic macromolecular protein structures, including subviral influenza particles and influenza VLP, in transformed plant cells or transformed insect cells.

The nucleic acid encoding the HA of influenza subtypes, for example but not limited to, A/New Caledonia/20/99 (H1N1), A/Indonesia/5/05 sub-type (H5N1), A/Brisbane/59/2007 (H1N1), A/Solomon Islands/3/2006 (H1N1), A/Singapore/1/57 (H2N2), A/Anhui/1/2005 (H5N1), A/Vietnam/1194/2004 (H5N1), A/Teal/Hong Kong/W312/97 (H6N1), A/Hong Kong/1073/99 (H9N2), A/Brisbane/10/2007 (H3N2), A/Wisconsin/67/2005 (H3N2), A/Equine/Prague/56 (H7N7), B/Malaysia/2506/2004, B/Florida/4/2006 may be expressed, for example, using a Baculovirus Expression System in an appropriate cell line, for example, *Spodoptera frugiperda* cells (e.g. Sf-9 cell line; ATCC PTA-4047). Other insect cell lines may also be used.

The nucleic acid encoding the HA may, alternately, be expressed in a plant cell, or in a plant. The nucleic acid encoding HA may be synthesized by reverse transcription and polymerase chain reaction (PCR) using HA RNA. As an example, the RNA may be isolated from human influenza A/New Caledonia/20/99 (H1N1) virus or human influenza A/Indonesia/5/05 (H5N1) virus, or other influenza viruses e.g. A/Brisbane/59/2007 (H1N1), A/Solomon Islands/3/2006 (H1N1), A/Singapore/1/57 (H2N2), A/Anhui/1/2005 (H5N1), A/Vietnam/1194/2004 (H5N1), A/Teal/Hong Kong/W312/97 (H6N1), A/Hong Kong/1073/99 (H9N2), A/Brisbane/10/2007 (H3N2), A/Wisconsin/67/2005 (H3N2), A/Equine/Prague/56 (H7N7), B/Malaysia/2506/2004, B/Florida/4/2006, or from cells infected with an influenza virus. For reverse transcription and PCR, oligonucleotide primers specific for HA RNA, for example but not limited to, human influenza A/New Caledonia/20/99 (H1N1) virus HA sequences or human influenza A/Indonesia/5/05 (H5N1) virus HA0 sequences, or HA sequences from influenza subtypes A/Brisbane/59/2007 (H1N1), A/Solomon Islands/3/2006 (H1N1), A/Singapore/1/57 (H2N2), A/Anhui/1/2005 (H5N1), A/Vietnam/1194/2004 (H5N1), A/Teal/Hong Kong/W312/97 (H6N1), A/Hong Kong/1073/99 (H9N2), A/Brisbane/10/2007 (H3N2), A/Wisconsin/67/2005 (H3N2), A/Equine/Prague/56 (H7N7), B/Malaysia/2506/2004, B/Florida/4/2006 may be used. Additionally, a nucleic acid encoding HA may be chemically synthesized using methods as would known to one of skill in the art.

The resulting cDNA copies of these genes may be cloned in a suitable expression vector as required by the host expression system. Examples of appropriate expression vectors for plants are described below, alternatively, baculovirus expression vector, for example, pFastBacI (InVitrogen), resulting in pFastBacI-based plasmids, using known methods, and information provided by the manufacturer's instructions may be used.

The present invention is further directed to a gene construct comprising a nucleic acid encoding HA, as described above, operatively linked to a regulatory element that is operative in a plant. Examples of regulatory elements operative in a plant cell and that may be used in accordance with the present invention include but are not limited to a plastocyanin regulatory region (U.S. Pat. No. 7,125,978; which is incorporated herein by reference), or a regulatory region of Ribulose 1,5-bisphosphate carboxylase/oxygenase (RuBisCO; U.S. Pat. No. 4,962,028; which is incorporated herein by reference), chlorophyll a/b binding protein (CAB; Leutwiler et al; 1986; which is incorporated herein by reference), ST-LS1 (associated with the oxygen-evolving complex of photosystem II and described by Stockhaus et al.

1987, 1989; which is incorporated herein by reference). An example of a plastocyanin regulatory region is a sequence comprising nucleotides 10-85 of SEQ ID NO: 36, or a similar region of any one of SEQ ID NOS: 37-47.

If the construct is expressed in an insect cell, examples of regulatory elements operative in an insect cell include but are not limited to the polyhedrin promoter (Possee and Howard 1987. Nucleic Acids Research 15:10233-10248), the gp64 promoter (Kogan et al, 1995. J Virology 69:1452-1461) and the like.

Therefore, an aspect of the invention provides for a nucleic acid comprising a regulatory region and a sequence encoding an influenza HA. The regulatory region may be a plastocyanin regulatory element, and the influenza HA may be selected from a group of influenza strains or subtypes, comprising A/New Caledonia/20/99 (H1N1), A/Indonesia/5/05 sub-type (H5N1), A/Brisbane/59/2007 (H1N1), A/Solomon Islands/3/2006 (H1N1), A/Singapore/1/57 (H2N2), A/Anhui/1/2005 (H5N1), A/Vietnam/1194/2004 (H5N1), A/Teal/Hong Kong/W312/97 (H6N1), A/Hong Kong/1073/99 (H9N2), A/Brisbane/10/2007 (H3N2), A/Wisconsin/67/2005 (H3N2), A/Equine/Prague/56 (H7N7), B/Malaysia/2506/2004, B/Florida/4/2006. Nucleic acid sequences comprising a plastocyanin regulatory element and an influenza HA are exemplified herein by SEQ ID NOS: 36-47.

It is known that there may be sequence differences in the sequence of influenza hemagglutinin amino acids sequences, or the nucleic acids encoding them, when influenza virus is cultured in eggs, or mammalian cells, (e.g. MDCK cells) or when isolated from an infected subject. Non-limiting examples of such differences are illustrated herein, including Example 18. Furthermore, as one of skill in the art would realize, additional variation may be observed within influenza hemagglutinins obtained from new strains as additional mutations continue to occur. Due to the known sequence variability between different influenza hemagglutinins, the present invention includes VLPs that may be made using any influenza hemagglutinin provided that when expressed in a host as described herein, the influenza hemagglutinin forms a VLP.

Sequence alignments and consensus sequences may be determined using any of several software packages known in the art, for example MULTALIN (F. CORPET, 1988, Nucl. Acids Res., 16 (22), 10881-10890), or sequences may be aligned manually and similarities and differences between the sequences determined.

The structure of hemagglutinins is well-studied and the structures are known to be highly conserved. When hemagglutinin structures are superimposed, a high degree of structural conservation is observed (rmsd<2A). This structural conservation is observed even though the amino acid sequence may vary in some positions (see, for example, Skehel and Wiley, 2000 Ann Rev Biochem 69:531-69; Vaccaro et al 2005). Regions of hemagglutinins are also well-conserved, for example:

Structural domains: The HA0 polyprotein is cleaved to provide mature HA. HA is a homotrimer with each monomer comprising a receptor binding domain (HA1) and a membrane-anchoring domain (HA2) linked by a single disulphide bond; the N-terminal 20 residues of the HA2 subunit may also be referred to as the HA fusion domain or sequence. A 'tail' region (internal to the membrane envelope) is also present. Each hemagglutinin comprises these regions or domains. Individual regions or domains are typically conserved in length.

All hemagglutinins contain the same number and position of intra- and inter-molecular disulfide bridges. The quantity and position on the amino acid sequence of the cysteines that participate in disulfide bridge network is conserved among the HAs. Examples of structures illustrating the characteristic intra- and intermolecular disulfide bridges and other conserved amino acids and their relative positions are described in, for example, Gamblin et al 2004 (Science 303:1838-1842). Exemplary structures and sequences include 1RVZ, 1RVX, 1RVT, 1RV0, 1RUY, 1RU7, available from the Protein Data Bank.

Cytoplasmic tail—the majority of hemagglutinins comprise 3 cysteines at conserved positions. One or more of these cysteines may be palmitoylated as a post-translational modification.

Amino acid variation is tolerated in hemagglutinins of influenza viruses. This variation provides for new strains that are continually identified. Infectivity between the new strains may vary. However, formation of hemagglutinin trimers, which subsequently form VLPs is maintained. The present invention, therefore, provides for a hemagglutinin amino acid sequence, or a nucleic acid encoding a hemag-

glutinin amino acid sequence, that forms VLPs in a plant, and includes known sequences and variant sequences that may develop.

FIG. 65 illustrates an example of such known variation. This figure shows a consensus amino acid sequence (SEQ ID NO: 74) for HA of the following H1N1 strains:

A/New Caledonia/20/99 (H1N1) (encoded by SEQ ID NO: 33),

A/Brisbane/59/2007 (H1N1) (SEQ ID NO: 48),

A/Solomon Islands/3/2006 (H1N1) (SEQ ID NO: 49) and

SEQ ID NO: 9. X1 (position 3) is A or V; X2 (position 52) is D or N; X3 (position 90) is K or R; X4 (position 99) is K or T; X5 (position 111) is Y or H; X6 (position 145) is V or T; X7 (position 154) is E or K; X8 (position 161) is R or K; X9 (position 181) is V or A; X10 (position 203) is D or N; X11 (position 205) is R or K; X12 (position 210) is T or K; X13 (position 225) is R or K; X14 (position 268) is W or R; X15 (position 283) is T or N; X16 (position 290) is E or K; X17 (position 432) is I or L; X18 (position 489) is N or D.

As another example of such variation, a sequence alignment and consensus sequence for HA of A/New Caledonia/20/99 (H1N1) (encoded by SEQ ID NO: 33), A/Brisbane/59/2007 (H1N1) (SEQ ID NO: 48), A/Solomon Islands/3/2006 (H1N1) (SEQ ID NO: 49), A/PuertoRico/8/34 (H1N1) and SEQ ID NO: 9 is shown below in Table 3.

TABLE 3

Sequence alignment and consensus sequence for HA of selected H1N1 strains					
SEQ ID NO.	Sequence				
	1				50
75	MKAKLLVLLC	TFTATYADTI	CIGYHANNST	DTVDTVLEKN	VTVTHSVNLL
9	MKAKLLVLLC	TFTATYADTI	CIGYHANNST	DTVDTVLEKN	VTVTHSVNLL
48	MKVKLLVLLC	TFTATYADTI	CIGYHANNST	DTVDTVLEKN	VTVTHSVNLL
49	MKVKLLVLLC	TFTATYADTI	CIGYHANNST	DTVDTVLEKN	VTVTHSVNLL
76	.....	.....	.....	.....	.....
Consensus	mkxkllvllc	tgatatyadti	cigyhannst	dtvdtvlekn	vtvthsvnll
	51				100
75	EDSHNGKLC	LKGIAPLQLG	NCSVAGWILG	NPECELLISK	ESWSYIVETP
9	EDSHNGKLC	LKGIAPLQLG	NCSVAGWILG	NPECELLISK	ESWSYIVETP
48	ENSHNGKLC	LKGIAPLQLG	NCSVAGWILG	NPECELLISK	ESWSYIVEKP
49	EDSHNGKLC	LKGIAPLQLG	NCSVAGWILG	NPECELLISR	ESWSYIVEKP
76	.....	.....	.....	.....	.....
Consensus	exshngklc1	lkgiaplqlg	ncsvagwilg	npecellis.	eswsyive.p
	101				150
75	NPENGTCPYG	YFADYEELRE	QLSSVSSFER	FEIFPKESSW	PNHTVTGVSA
9	NPENGTCPYG	YFADYEELRE	QLSSVSSFER	FEIFPKESSW	PNHTVTGVSA
48	NPENGTCPYG	HFADYEELRE	QLSSVSSFER	FEIFPKESSW	PNHTVTGVSA
49	NPENGTCPYG	HFADYEELRE	QLSSVSSFER	FEIFPKESSW	PNHTTGVSA
76	.....	.....	.....	.....	.....
Consensus	npengtcpyg	xfadyeelre	qlssvssfer	feifpkessw	pnhtxtgvsa
	151				200
75	SCSHNGKSSF	YRNLLWLTGK	NGLYPNLSKS	YVNNKEKEVL	VLWGVHHPPN
9	SCSHNGKSSF	YRNLLWLTGK	NGLYPNLSKS	YVNNKEKEVL	VLWGVHHPPN
48	SCSHNGESSF	YRNLLWLTGK	NGLYPNLSKS	YANNKEKEVL	VLWGVHHPPN
49	SCSHNGESSF	YKNNLWLTGK	NGLYPNLSKS	YANNKEKEVL	VLWGVHHPPN
76	.....	.....	.....	.....	.....
Consensus	scshngxssf	yxnllwltgk	nglypnlsks	yxnnkekevl	vlwgvhhppn
	201				250
75	IGNQRALYHT	ENAYVSVVSS	HYSRRFTPEI	AKRPKVRDQE	GRINYWTLL
9	IGNQRALYHT	ENAYVSVVSS	HYSRRFTPEI	AKRPKVRDQE	GRINYWTLL
48	IGDQRALYHT	ENAYVSVVSS	HYSRKFTPEI	AKRPKVRDQE	GRINYWTLL
49	IGDQRALYHK	ENAYVSVVSS	HYSRKFTPEI	AKRPKVRDQE	GRINYWTLL
76	.....	.....	.....	.....	.....
Consensus	igxqxalyhx	enayvsvvss	hysrxftpeI	akrpkvr#qe	gRi#yywtll

TABLE 3-continued

Sequence alignment and consensus sequence for HA of selected H1N1 strains				
SEQ ID NO.	Sequence			
	251			300
75	EPGDTIIFEA	NGNLIAPWYA	FALSRGFGSG	IITSNAPMDE CDAKCQTPQG
9	EPGDTIIFEA	NGNLIAPWYA	FALSRGFGSG	IITSNAPMDE CDAKCQTPQG
48	EPGDTIIFEA	NGNLIAPRYA	FALSRGFGSG	IINSNAPMDK CDAKCQTPQG
49	EPGDTIIFEA	NGNLIAPRYA	FALSRGFGSG	IINSNAPMDE CDAKCQTPQG
76	NTDLEVLMEW	...LKTRPIL	SPLTKGILGF	VFTLTVPSEER GLQRRRFVQN
Consensus	#pgdt!ifEa	ngnLiapxya	faLsrGfgsg	!itsnaPm#x cdakcqtPqG
	301			350
75	AINSSLPFQ	VHPVTIGEC	KYVRSACLRLM	VT.GLRNIPS IQSRGLFGAI
9	AINSSLPFQ	VHPVTIGEC	KYVRSACLRLM	VT.GLRNIPS IQSRGLFGAI
48	AINSSLPFQ	VHPVTIGEC	KYVRSACLRLM	VT.GLRNIPS IQSRGLFGAI
49	AINSSLPFQ	VHPVTIGEC	KYVRSACLRLM	VT.GLRNIPS IQSRGLFGAI
76	ALNG....N	GDPNNMDKAV	KLYRKLKREI	TFHGAKAISL SYSAGALASC
Consensus	AiNsslPfqN	vhPvtigecP	KyvRsaKlrm	vtxGlr#Ips iqSrGlfgai
	351			400
75	AGFIEGGWTG	MVDGWYGYHH	QNEQSGYAA	DQKSTQNAIN GITNKVNSVI
9	AGFIEGGWTG	MVDGWYGYHH	QNEQSGYAA	DQKSTQNAIN GITNKVNSVI
48	AGFIEGGWTG	MVDGWYGYHH	QNEQSGYAA	DQKSTQNAIN GITNKVNSVI
49	AGFIEGGWTG	MVDGWYGYHH	QNEQSGYAA	DQKSTQNAIN GITNKVNSVI
76	MGLIYNRM.G	AVTTEVAFGL	VCATCEQIAD	SQHRSHRQMV TTTNPLIRHE
Consensus	aGfIeggwtG	mVdgwyg%hh	qneqsgyAa	dQkstqnain giTnkvnsvi
	401			450
75	EKMNTQFTAV	GKEFNKLERR	MENLNKKVDD	GFLDIWTYNA ELLVLENER
9	EKMNTQFTAV	GKEFNKLERR	MENLNKKVDD	GFLDIWTYNA ELLVLENER
48	EKMNTQFTAV	GKEFNKLERR	MENLNKKVDD	GFIDIWTYNA ELLVLENER
49	EKMNTQFTAV	GKEFNKLERR	MENLNKKVDD	GFIDIWTYNA ELLVLENER
76	NRMVLASTTA	.KAMEQMAGS	SEQAAEAMEV	A.....S QARQMVQAMR
Consensus	#kMntqfTav	gKef#k\$err	mE#lnkkv#d	gfdiwtyna #llv\$l#neR
	451			500
75	TLDFHDSNVK	NLYEKVKSQ	KNNAKEIGNG	CFEFYHKCNN ECMESVKNGT
9	TLDFHDSNVK	NLYEKVKSQ	KNNAKEIGNG	CFEFYHKCNN ECMESVKNGT
48	TLDFHDSNVK	NLYEKVKSQ	KNNAKEIGNG	CFEFYHKCND ECMESVKNGT
49	TLDFHDSNVK	NLYEKVKSQ	KNNAKEIGNG	CFEFYHKCND ECMESVKNGT
76	TIGTHPSSSA	GLKNDLLENL	QAYQKRMGVQ	MQRFK.....
Consensus	TldfHdSnvk	nLy#kvks#L	knnaKeiGng	cfeFyhkcnx ecmesvkngt
	501			550
75	YDYPKYSEES	KLNREKIDGV	KLESMGVYQI	LAIYSTVASS LVLLVSLGAI
9	YDYPKYSEES	KLNREKIDGV	KLESMGVYQI	LAIYSTVASS LVLLVSLGAI
48	YDYPKYSEES	KLNREKIDGV	KLESMGVYQI	LAIYSTVASS LVLLVSLGAI
49	YDYPKYSEES	KLNREKIDGV	KLESMGVYQI	LAIYSTVASS LVLLVSLGAI
76	.....	.....	.....	.....
Consensus	ydypkysees	lnkrekidgv	klesmgvyqi	laiystvass lvllvslgai
	551	566		
75	SFWMCSNGSL	QCRICI		
9	SFWMCSNGSL	QCRICI		
48	SFWMCSNGSL	QCRICI		
49	SFWMCSNGSL	QCRICI		
76	.....	.....		
Consensus	sfwmcsngsl	qcrici		

The consensus sequence indicates in upper case letters amino acids common to all sequences at a designated position; lower case letters indicate amino acids common to at least half, or a majority of the sequences; the symbol ! is any one of I or V; the symbol \$ is any one of L or M; the symbol % is any one of F or Y; the symbol # is any one of N, D, Q, E, B or Z; the symbol “.” is no amino acid (e.g. a deletion); X at position 3 is any one of A or V; X at position 52 is any one of E or N; X at position 90 is K or R; X at position 99 is T or K; X at position 111 is any one of Y or H; X at position 145 is any one of V or T; X at position 157

is K or E; X at position 162 is R or K; X at position 182 is V or A; X at position 203 is N or D; X at position 205 is R or K; X at position 210 is T or K; X at position 225 is K or Y; X at position 333 is H or a deletion; X at position 433 is I or L; X at position 49) is N or D.

As another example of such variation, a sequence alignment and consensus sequence for HA of A/Anhui/1/2005 (H5N1) (SEQ ID NO: 55), A/Vietnam/1194/2004 (H5N1) and A/Indonesia/5/2006 (H5N1) (SEQ ID NO: 10) is shown below in Table 4.

TABLE 4

Sequence alignment and consensus sequence for HA of selected H1N1 strains				
SEQ ID NO.	Sequence			
1	50			
10	MEKIVLLLAI	VSLVKS	DQIC	IGYHANNSTE QVDTIMEKNV TVTHAQDILE
56	MEKIVLLFAI	VSLVKS	DQIC	IGYHANNSTE QVDTIMEKNV TVTHAQDILE
55	MEKIVLLLAI	VSLVKS	DQIC	IGYHANNSTE QVDTIMEKNV TVTHAQDILE
Consensus	MEKIVLLLAI	VSLVKS	DQIC	IGYHANNSTE QVDTIMEKNV TVTHAQDILE
51	100			
10	KTHNGKLCDL	DGVKPLILRD	CSVAGWLLGN	PMCDEFINVP EWSYIVEKAN
56	KTHNGKLCDL	DGVKPLILRD	CSVAGWLLGN	PMCDEFINVP EWSYIVEKAN
55	KTHNGKLCDL	DGVKPLILRD	CSVAGWLLGN	PMCDEFINVP EWSYIVEKAN
Consensus	KTHNGKLCDL	DGVKPLILRD	CSVAGWLLGN	PMCDEFINVP EWSYIVEKAN
101	150			
10	PTNDLCYPGS	FNDYEELKHL	LSRINHFEKI	QIIPKSSWSD HEASSGVSSA
56	PVNDLCYPGD	FNDYEELKHL	LSRINHFEKI	QIIPSKKWS HEASLGVSSA
55	PANDLCYPGN	FNDYEELKHL	LSRINHFEKI	QIIPKSSWSD HEASSGVSSA
Consensus	PxNDLCYPGx	FNDYEELKHL	LSRINHFEKI	QIIPSKKWSd HEASsGVSSA
151	200			
10	CPYLGSPSFF	RNVVWLKKN	STYPTIKKSY	NNTNQEDLLV LWGIHHPNDA
56	CPYQKSSFF	RNVVWLKKN	STYPTIKRSY	NNTNQEDLLV LWGIHHPNDA
55	CPYQGTSPFF	RNVVWLKKN	NTYPTIKRSY	NNTNQEDLLI LWGIHHSNDA
Consensus	CPYqGxpSFF	RNVVWLKKN	sTYPTIKrSY	NNTNQEDLL! LWGIHhpNDA
201	250			
10	AEQTRLQYQN	TTYISIGTST	LNQRLVPKIA	TRSKVNGQSG RMEFFWTILK
56	AEQTkLYQN	TTYISVGTST	LNQRLVPRIA	TRSKVNGQSG RMEFFWTILK
55	AEQTKLYQN	TTYISVGTST	LNQRLVPKIA	TRSKVNGQSG RMDFFWTILK
Consensus	AEQTkLYQN	TTYIS!GTST	LNQRLVPkIA	TRSKVNGQSG RM#FFWTILK
251	300			
10	PNDAINFESN	GNFIAPEYAY	KIVKKGDSAI	MKSELEYGNC NTKCQTPMGA
56	PNDAINFESN	GNFIAPEYAY	KIVKKGDSI	MKSELEYGNC NTKCQTPMGA
55	PNDAINFESN	GNFIAPEYAY	KIVKKGDSAI	VKSEVEYGNC NTKCQTPIGA
Consensus	PNDAINFESN	GNFIAPEYAY	KIVKKGDSaI	mKSELEYGNC NTKCQTPmGA
301	350			
10	INSSMPFHNI	HPLTIGECPK	YVKSrNLVLA	TGLRNSPQRE SRRKKRGLFG
56	INSSMPFHNI	HPLTIGECPK	YVKSrNLVLA	TGLRNSPQRE RRRKKRGLFG
55	INSSMPFHNI	HPLTIGECPK	YVKSrNLVLA	TGLRNSPLRE RRRK.RGLFG
Consensus	INSSMPFHNI	HPLTIGECPK	YVKSrNLVLA	TGLRNSPqRE rRRK:rGLFG
351	400			
10	AIAGFIEGGW	QGMVDGWYGY	HHSNEQGSY	AADKESTQKA IDGVTNKVNS
56	AIAGFIEGGW	QGMVDGWYGY	HHSNEQGSY	AADKESTQKA IDGVTNKVNS
55	AIAGFIEGGW	QGMVDGWYGY	HHSNEQGSY	AADKESTQKA IDGVTNKVNS
Consensus	AIAGFIEGGW	QGMVDGWYGY	HHSNEQGSY	AADKESTQKA IDGVTNKVNS
401	450			
10	IIDKMNTQFE	AVGREFNNLE	RRIENLNKKM	EDGFLDVWTY NAELLVLMEN
56	IIDKMNTQFE	AVGREFNNLE	RRIENLNKKM	EDGFLDVWTY NAELLVLMEN
55	IIDKMNTQFE	AVGREFNNLE	RRIENLNKKM	EDGFLDVWTY NAELLVLMEN
Consensus	IIDKMNTQFE	AVGREFNNLE	RRIENLNKKM	EDGFLDVWTY NAELLVLMEN
451	500			
10	ERTLDFHDSN	VKNLYDKVRL	QLRDNAKELG	NGCFEFYHKC DNECMESIRN
56	ERTLDFHDSN	VKNLYDKVRL	QLRDNAKELG	NGCFEFYHKC DNECMESVRN
55	ERTLDFHDSN	VKNLYDKVRL	QLRDNAKELG	NGCFEFYHKC DNECMESVRN
Consensus	ERTLDFHDSN	VKNLYDKVRL	QLRDNAKELG	NGCFEFYHKC DNECMES!RN
501	550			
10	GTYNYPQYSE	EARLKREEIS	GVKLESIGTY	QILSIYSTVA SSLALAIMMA
56	GTYDYPQYSE	EARLKREEIS	GVKLESIGTY	QILSIYSTVA SSLALAIMVA
55	GTYDYPQYSE	EARLKREEIS	GVKLESIGTY	QILSIYSTVA SSLALAIMVA
Consensus	GTY#YPQYSE	EARLKREEIS	GVKLESIGTY	QILSIYSTVA SSLALAIMvA
551	568			
10	GLSLWMCNSG	SLQCRICI		
56	GLSLWMCNSG	SLQCRICI		
55	GLSLWMCNSG	SLQCRICI		
Consensus	GLSLWMCNSG	SLQCRICI		

The consensus sequence indicates in upper case letters amino acids common to all sequences at a designated position; lower case letters indicate amino acids common to at least half, or a majority of the sequences; the symbol ! is any one of I or V; the symbol \$ is any one of L or M; the symbol % is any one of F or Y; the symbol # is any one of N, D, Q, E, B or Z; X at position 102 is any of T, V or A; X t position 110 is any of S, D or N; X at position 156 is any of S, K or T.

The above-illustrated and described alignments and consensus sequences are non-limiting examples of variants in hemagglutinin amino acid sequences that may be used in various embodiments of the invention for the production of VLPs in a plant.

A nucleic acid encoding an amino acid sequence may be easily determined, as the codons for each amino acid are known in the art. Provision of an amino acid sequence, therefore, teaches the degenerate nucleic acid sequences that encode it. The present invention, therefore, provides for a nucleic acid sequence encoding the hemagglutinin of those influenza strains and subtypes disclosed herein (e.g. A/New Caledonia/20/99 (H1N1)A/Indonesia/5/2006 (H5N1), A/chicken/New York/1995, A/herring gull/DE/677/88 (H2N8), A/Texas/32/2003, A/mallard/MN/33/00, A/duck/Shanghai/1/2000, A/northern pintail/TX/828189/02, A/Turkey/Ontario/6118/68(H8N4), A/shoveler/Iran/G54/03, A/chicken/Germany/N/1949(H10N7), A/duck/England/56 (H11N6), A/duck/Alberta/60/76(H12N5), A/Gull/Maryland/704/77(H13N6), A/Mallard/Gurjev/263/82, A/duck/Australia/341/83 (H15N8), A/black-headed gull/Sweden/5/99 (H16N3), B/Lee/40, C/Johannesburg/66, A/PuertoRico/8/34 (H1N1), A/Brisbane/59/2007 (H1N1), A/Solomon Islands 3/2006 (H1N1), A/Brisbane 10/2007 (H3N2), A/Wisconsin/67/2005 (H3N2), B/Malaysia/2506/2004, B/Florida/4/2006, A/Singapore/1/57 (H2N2), A/Anhui/1/2005 (H5N1), A/Vietnam/1194/2004 (H5N1), A/Teal/HongKong/W312/97 (H6N1), A/Equine/Prague/56 (H7N7), A/HongKong/1073/99 (H9N2)), as well as the degenerate sequences that encode the above hemagglutinins.

Further, an amino acid sequence encoded by a nucleic acid may be easily determined, as the codon or codons for each amino acid are known. Provision of a nucleic acid, therefore, teaches an amino acid sequence encoded by it. The invention, therefore, provides for amino acid sequences of the hemagglutinin of those influenza strains and subtypes disclosed herein those disclosed herein (e.g. A/New Caledonia/20/99 (H1N1)A/Indonesia/5/2006 (H5N1), A/chicken/New York/1995, A/herring gull/DE/677/88 (H2N8), A/Texas/32/2003, A/mallard/MN/33/00, A/duck/Shanghai/1/2000, A/northern pintail/TX/828189/02, A/Turkey/Ontario/6118/68(H8N4), A/shoveler/Iran/G54/03, A/chicken/Germany/N/1949(H10N7), A/duck/England/56 (H11N6), A/duck/Alberta/60/76(H12N5), A/Gull/Maryland/704/77(H13N6), A/Mallard/Gurjev/263/82, A/duck/Australia/341/83 (H15N8), A/black-headed gull/Sweden/5/99 (H16N3), B/Lee/40, C/Johannesburg/66, A/PuertoRico/8/34 (H1N1), A/Brisbane/59/2007 (H1N1), A/Solomon Islands 3/2006 (H1N1), A/Brisbane 10/2007 (H3N2), A/Wisconsin/67/2005 (H3N2), B/Malaysia/2506/2004, B/Florida/4/2006, A/Singapore/1/57 (H2N2), A/Anhui/1/2005 (H5N1), A/Vietnam/1194/2004 (H5N1), A/Teal/HongKong/W312/97 (H6N1), A/Equine/Prague/56 (H7N7), A/HongKong/1073/99 (H9N2)).

In plants, influenza VLPs bud from the plasma membrane (see Example 5, and FIG. 19) therefore the lipid composition of the VLPs reflects their origin. The VLPs produced according to the present invention comprise HA of one or more

than one type or subtype of influenza, complexed with plant derived lipids. Plant lipids can stimulate specific immune cells and enhance the immune response induced. Plant membranes are made of lipids, phosphatidylcholine (PC) and phosphatidylethanolamine (PE), and also contain glycosphingolipids, saponins, and phytosterols. Additionally, lipid rafts are also found in plant plasma membranes—these microdomains are enriched in sphingolipids and sterols. In plants, a variety of phytosterols are known to occur, including stigmasterol, sitosterol, 24-methylcholesterol and cholesterol (Mongrand et al., 2004).

PC and PE, as well as glycosphingolipids can bind to CD1 molecules expressed by mammalian immune cells such as antigen-presenting cells (APCs) like dendritic cells and macrophages and other cells including B and T lymphocytes in the thymus and liver (Tsuji M., 2006). CD1 molecules are structurally similar to major histocompatibility complex (MHC) molecules of class I and their role is to present glycolipid antigens to NKT cells (Natural Killer T cells). Upon activation, NKT cells activate innate immune cells such as NK cells and dendritic cells and also activate adaptive immune cells like the antibody-producing B cells and T-cells.

A variety of phytosterols may be found in a plasma membrane—the specific complement may vary depending on the species, growth conditions, nutrient resources or pathogen state, to name a few factors. Generally, beta-sitosterol is the most abundant phytosterol.

The phytosterols present in an influenza VLP complexed with a lipid bilayer, such as an plasma-membrane derived envelope may provide for an advantageous vaccine composition. Without wishing to be bound by theory, plant-made VLPs complexed with a lipid bilayer, such as a plasma-membrane derived envelope, may induce a stronger immune reaction than VLPs made in other expression systems, and may be similar to the immune reaction induced by live or attenuated whole virus vaccines.

Therefore, in some embodiments, the invention provides for a VLP complexed with a plant-derived lipid bilayer. In some embodiments the plant-derived lipid bilayer may comprise the envelope of the VLP.

The VLP produced within a plant may induce an HA comprising plant-specific N-glycans. Therefore, this invention also provides for a VLP comprising HA having plant specific N-glycans.

Furthermore, modification of N-glycan in plants is known (see for example U.S. 60/944,344; which is incorporated herein by reference) and HA having modified N-glycans may be produced. HA comprising a modified glycosylation pattern, for example with reduced fucosylated, xylosylated, or both, fucosylated and xylosylated, N-glycans may be obtained, or HA having a modified glycosylation pattern may be obtained, wherein the protein lacks fucosylation, xylosylation, or both, and comprises increased galactosylation. Furthermore, modulation of post-translational modifications, for example, the addition of terminal galactose may result in a reduction of fucosylation and xylosylation of the expressed HA when compared to a wild-type plant expressing HA.

For example, which is not to be considered limiting, the synthesis of HA having a modified glycosylation pattern may be achieved by co-expressing the protein of interest along with a nucleotide sequence encoding beta-1.4galactosyltransferase (GalT), for example, but not limited to mammalian GalT, or human GalT however GalT from another sources may also be used. The catalytic domain of GalT may also be fused to a CTS domain (i.e. the cytoplasm-

mic tail, transmembrane domain, stem region) of N-acetylglucosaminyl transferase (GNT1), to produce a GNT1-GaIT hybrid enzyme, and the hybrid enzyme may be co-expressed with HA. The HA may also be co-expressed along with a nucleotide sequence encoding N-acetylglucosaminyltransferase III (GnT-III), for example but not limited to mammalian GnT-III or human GnT-III, GnT-III from other sources may also be used. Additionally, a GNT1-GnT-III hybrid enzyme, comprising the CTS of GNT1 fused to GnT-III may also be used.

Therefore the present invention also includes VLP's comprising HA having modified N-glycans.

Without wishing to be bound by theory, the presence of plant N-glycans on HA may stimulate the immune response by promoting the binding of HA by antigen presenting cells. Stimulation of the immune response using plant N glycan has been proposed by Saint-jore-Dupas et al. (2007). Furthermore, the conformation of the VLP may be advantageous for the presentation of the antigen, and enhance the adjuvant effect of VLP when complexed with a plant derived lipid layer.

By "regulatory region" "regulatory element" or "promoter" it is meant a portion of nucleic acid typically, but not always, upstream of the protein coding region of a gene, which may be comprised of either DNA or RNA, or both DNA and RNA. When a regulatory region is active, and in operative association, or operatively linked, with a gene of interest, this may result in expression of the gene of interest. A regulatory element may be capable of mediating organ specificity, or controlling developmental or temporal gene activation. A "regulatory region" includes promoter elements, core promoter elements exhibiting a basal promoter activity, elements that are inducible in response to an external stimulus, elements that mediate promoter activity such as negative regulatory elements or transcriptional enhancers. "Regulatory region", as used herein, also includes elements that are active following transcription, for example, regulatory elements that modulate gene expression such as translational and transcriptional enhancers, translational and transcriptional repressors, upstream activating sequences, and mRNA instability determinants. Several of these latter elements may be located proximal to the coding region.

In the context of this disclosure, the term "regulatory element" or "regulatory region" typically refers to a sequence of DNA, usually, but not always, upstream (5') to the coding sequence of a structural gene, which controls the expression of the coding region by providing the recognition for RNA polymerase and/or other factors required for transcription to start at a particular site. However, it is to be understood that other nucleotide sequences, located within introns, or 3' of the sequence may also contribute to the regulation of expression of a coding region of interest. An example of a regulatory element that provides for the recognition for RNA polymerase or other transcriptional factors to ensure initiation at a particular site is a promoter element. Most, but not all, eukaryotic promoter elements contain a TATA box, a conserved nucleic acid sequence comprised of adenosine and thymidine nucleotide base pairs usually situated approximately 25 base pairs upstream of a transcriptional start site. A promoter element comprises a basal promoter element, responsible for the initiation of transcription, as well as other regulatory elements (as listed above) that modify gene expression.

There are several types of regulatory regions, including those that are developmentally regulated, inducible or constitutive. A regulatory region that is developmentally regulated, or controls the differential expression of a gene under

its control, is activated within certain organs or tissues of an organ at specific times during the development of that organ or tissue. However, some regulatory regions that are developmentally regulated may preferentially be active within certain organs or tissues at specific developmental stages, they may also be active in a developmentally regulated manner, or at a basal level in other organs or tissues within the plant as well. Examples of tissue-specific regulatory regions, for example see-specific a regulatory region, include the napin promoter, and the cruciferin promoter (Rask et al., 1998, J. Plant Physiol. 152: 595-599; Bilodeau et al., 1994, Plant Cell 14: 125-130). An example of a leaf-specific promoter includes the plastocyanin promoter (FIG. 1b or SEQ ID NO:23); U.S. Pat. No. 7,125,978, which is incorporated herein by reference).

An inducible regulatory region is one that is capable of directly or indirectly activating transcription of one or more DNA sequences or genes in response to an inducer. In the absence of an inducer the DNA sequences or genes will not be transcribed. Typically the protein factor that binds specifically to an inducible regulatory region to activate transcription may be present in an inactive form, which is then directly or indirectly converted to the active form by the inducer. However, the protein factor may also be absent. The inducer can be a chemical agent such as a protein, metabolite, growth regulator, herbicide or phenolic compound or a physiological stress imposed directly by heat, cold, salt, or toxic elements or indirectly through the action of a pathogen or disease agent such as a virus. A plant cell containing an inducible regulatory region may be exposed to an inducer by externally applying the inducer to the cell or plant such as by spraying, watering, heating or similar methods. Inducible regulatory elements may be derived from either plant or non-plant genes (e.g. Gatz, C. and Lenk, I. R. P., 1998, Trends Plant Sci. 3, 352-358; which is incorporated by reference). Examples, of potential inducible promoters include, but not limited to, tetracycline-inducible promoter (Gatz, C., 1997, Ann. Rev. Plant Physiol. Plant Mol. Biol. 48, 89-108; which is incorporated by reference), steroid inducible promoter (Aoyama, T. and Chua, N. H., 1997, Plant J. 2, 397-404; which is incorporated by reference) and ethanol-inducible promoter (Salter, M. G., et al, 1998, Plant Journal 16, 127-132; Caddick, M. X., et al, 1998, Nature Biotech. 16, 177-180, which are incorporated by reference) cytokinin inducible IB6 and CK11 genes (Brandstatter, I. and Kieber, J. J., 1998, Plant Cell 10, 1009-1019; Kakimoto, T., 1996, Science 274, 982-985; which are incorporated by reference) and the auxin inducible element, DR5 (Ulmasov, T., et al., 1997, Plant Cell 9, 1963-1971; which is incorporated by reference).

A constitutive regulatory region directs the expression of a gene throughout the various parts of a plant and continuously throughout plant development. Examples of known constitutive regulatory elements include promoters associated with the CaMV 35S transcript. (Odell et al., 1985, Nature, 313: 810-812), the rice actin 1 (Zhang et al, 1991, Plant Cell, 3: 1155-1165), actin 2 (An et al., 1996, Plant J., 10: 107-121), or tms 2 (U.S. Pat. No. 5,428,147, which is incorporated herein by reference), and triosephosphate isomerase 1 (Xu et. al., 1994, Plant Physiol. 106: 459-467) genes, the maize ubiquitin 1 gene (Cornejo et al, 1993, Plant Mol. Biol. 29: 637-646), the *Arabidopsis* ubiquitin 1 and 6 genes (Holtorf et al, 1995, Plant Mol. Biol. 29: 637-646), and the tobacco translational initiation factor 4A gene (Mandel et al, 1995 Plant Mol. Biol. 29: 995-1004). The term "constitutive" as used herein does not necessarily indicate that a gene under control of the constitutive regulatory

region is expressed at the same level in all cell types, but that the gene is expressed in a wide range of cell types even though variation in abundance is often observed.

By "operatively linked" it is meant that the particular sequences, for example a regulatory element and a coding region of interest, interact either directly or indirectly to carry out an intended function, such as mediation or modulation of gene expression. The interaction of operatively linked sequences may, for example, be mediated by proteins that interact with the operatively linked sequences.

The one or more than one nucleotide sequence of the present invention may be expressed in any suitable plant host that is transformed by the nucleotide sequence, or constructs, or vectors of the present invention. Examples of suitable hosts include, but are not limited to, agricultural crops including alfalfa, canola, *Brassica* spp., maize, *Nicotiana* spp., alfalfa, potato, ginseng, pea, oat, rice, soybean, wheat, barley, sunflower, cotton and the like.

The one or more chimeric genetic constructs of the present invention can further comprise a 3' untranslated region. A 3' untranslated region refers to that portion of a gene comprising a DNA segment that contains a polyadenylation signal and any other regulatory signals capable of effecting mRNA processing or gene expression. The polyadenylation signal is usually characterized by effecting the addition of polyadenylic acid tracks to the 3' end of the mRNA precursor. Polyadenylation signals are commonly recognized by the presence of homology to the canonical form 5' AATAAA-3' although variations are not uncommon. One or more of the chimeric genetic constructs of the present invention can also include further enhancers, either translation or transcription enhancers, as may be required. These enhancer regions are well known to persons skilled in the art, and can include the ATG initiation codon and adjacent sequences. The initiation codon must be in phase with the reading frame of the coding sequence to ensure translation of the entire sequence.

Non-limiting examples of suitable 3' regions are the 3' transcribed non-translated regions containing a polyadenylation signal of *Agrobacterium* tumor inducing (Ti) plasmid genes, such as the nopaline synthase (Nos gene) and plant genes such as the soybean storage protein genes, the small subunit of the ribulose-1, 5-bisphosphate carboxylase (ssRUBISCO; U.S. Pat. No. 4,962,028; which is incorporated herein by reference) gene, the promoter used in regulating plastocyanin expression (Pwee and Gray 1993; which is incorporated herein by reference). An example of a plastocyanin promoter is described in U.S. Pat. No. 7,125,978 (which is incorporated herein by reference)

As described herein, promoters comprising enhancer sequences with demonstrated efficiency in leaf expression, have been found to be effective in transient expression. Without wishing to be bound by theory, attachment of upstream regulatory elements of a photosynthetic gene by attachment to the nuclear matrix may mediate strong expression. For example up to -784 from the translation start site of the pea plastocyanin gene may be used mediate strong reporter gene expression.

To aid in identification of transformed plant cells, the constructs of this invention may be further manipulated to include plant selectable markers. Useful selectable markers include enzymes that provide for resistance to chemicals such as an antibiotic for example, gentamycin, hygromycin, kanamycin, or herbicides such as phosphinothrycin, glyphosate, chlorosulfuron, and the like. Similarly, enzymes providing for production of a compound identifiable by colour

change such as GUS (beta-glucuronidase), or luminescence, such as luciferase or GFP, may be used.

Also considered part of this invention are transgenic plants, plant cells or seeds containing the chimeric gene construct of the present invention. Methods of regenerating whole plants from plant cells are also known in the art. In general, transformed plant cells are cultured in an appropriate medium, which may contain selective agents such as antibiotics, where selectable markers are used to facilitate identification of transformed plant cells. Once callus forms, shoot formation can be encouraged by employing the appropriate plant hormones in accordance with known methods and the shoots transferred to rooting medium for regeneration of plants. The plants may then be used to establish repetitive generations, either from seeds or using vegetative propagation techniques. Transgenic plants can also be generated without using tissue cultures.

Also considered part of this invention are transgenic plants, trees, yeast, bacteria, fungi, insect and animal cells containing the chimeric gene construct comprising a nucleic acid encoding recombinant HAO for VLP production, in accordance with the present invention.

The regulatory elements of the present invention may also be combined with coding region of interest for expression within a range of host organisms that are amenable to transformation, or transient expression. Such organisms include, but are not limited to plants, both monocots and dicots, for example but not limited to corn, cereal plants, wheat, barley, oat, *Nicotiana* spp, *Brassica* spp, soybean, bean, pea, alfalfa, potato, tomato, ginseng, and *Arabidopsis*.

Methods for stable transformation, and regeneration of these organisms are established in the art and known to one of skill in the art. The method of obtaining transformed and regenerated plants is not critical to the present invention.

By "transformation" it is meant the stable interspecific transfer of genetic information (nucleotide sequence) that is manifested genotypically, phenotypically or both. The interspecific transfer of genetic information from a chimeric construct to a host may be heritable and the transfer of genetic information considered stable, or the transfer may be transient and the transfer of genetic information is not inheritable.

By the term "plant matter", it is meant any material derived from a plant. Plant matter may comprise an entire plant, tissue, cells, or any fraction thereof. Further, plant matter may comprise intracellular plant components, extracellular plant components, liquid or solid extracts of plants, or a combination thereof. Further, plant matter may comprise plants, plant cells, tissue, a liquid extract, or a combination thereof, from plant leaves, stems, fruit, roots or a combination thereof. Plant matter may comprise a plant or portion thereof which has not been subjected to any processing steps. However, it is also contemplated that the plant material may be subjected to minimal processing steps as defined below, or more rigorous processing, including partial or substantial protein purification using techniques commonly known within the art including, but not limited to chromatography, electrophoresis and the like.

By the term "minimal processing" it is meant plant matter, for example, a plant or portion thereof comprising a protein of interest which is partially purified to yield a plant extract, homogenate, fraction of plant homogenate or the like (i.e. minimally processed). Partial purification may comprise, but is not limited to disrupting plant cellular structures thereby creating a composition comprising soluble plant components, and insoluble plant components which may be separated for example, but not limited to, by centrifugation,

filtration or a combination thereof. In this regard, proteins secreted within the extracellular space of leaf or other tissues could be readily obtained using vacuum or centrifugal extraction, or tissues could be extracted under pressure by passage through rollers or grinding or the like to squeeze or liberate the protein free from within the extracellular space. Minimal processing could also involve preparation of crude extracts of soluble proteins, since these preparations would have negligible contamination from secondary plant products. Further, minimal processing may involve aqueous extraction of soluble protein from leaves, followed by precipitation with any suitable salt. Other methods may include large scale maceration and juice extraction in order to permit the direct use of the extract.

The plant matter, in the form of plant material or tissue may be orally delivered to a subject. The plant matter may be administered as part of a dietary supplement, along with other foods, or encapsulated. The plant matter or tissue may also be concentrated to improve or increase palatability, or provided along with other materials, ingredients, or pharmaceutical excipients, as required.

Examples of a subject or target organism that the VLPs of the present invention may be administered to include, but are not limited to, humans, primates, birds, water fowl, migratory birds, quail, duck, geese, poultry, chicken, swine, sheep, equine, horse, camel, canine, dogs, feline, cats, tiger, leopard, civet, mink, stone marten, ferrets, house pets, livestock, rabbits, mice, rats, guinea pigs or other rodents, seal, whale and the like. Such target organisms are exemplary, and are not to be considered limiting to the applications and uses of the present invention.

It is contemplated that a plant comprising the protein of interest, or expressing the VLP comprising the protein of interest may be administered to a subject or target organism, in a variety of ways depending upon the need and the situation. For example, the protein of interest obtained from the plant may be extracted prior to its use in either a crude, partially purified, or purified form. If the protein is to be purified, then it may be produced in either edible or non-edible plants. Furthermore, if the protein is orally administered, the plant tissue may be harvested and directly feed to the subject, or the harvested tissue may be dried prior to feeding, or an animal may be permitted to graze on the plant with no prior harvest taking place. It is also considered within the scope of this invention for the harvested plant tissues to be provided as a food supplement within animal feed. If the plant tissue is being feed to an animal with little or not further processing it is preferred that the plant tissue being administered is edible.

Post-transcriptional gene silencing (PTGS) may be involved in limiting expression of transgenes in plants, and co-expression of a suppressor of silencing from the potato virus Y (HcPro) may be used to counteract the specific degradation of transgene mRNAs (Brigneti et al., 1998). Alternate suppressors of silencing are well known in the art and may be used as described herein (Chiba et al., 2006, *Virology* 346:7-14; which is incorporated herein by reference), for example but not limited to, TEV-p1/HC-Pro (Tobacco etch virus-p1/HC-Pro), BYV-p21, p19 of Tomato bushy stunt virus (TBSV p19), capsid protein of Tomato crinkle virus (TCV-CP), 2b of Cucumber mosaic virus; CMV-2b), p25 of Potato virus X (PVX-p25), p11 of Potato virus M (PVM-p11), p11 of Potato virus S (PVS-p11), p16 of Blueberry scorch virus, (BScV-p16), p23 of Citrus tristexa virus (CTV-p23), p24 of Grapevine leafroll-associated virus-2, (GLRaV-2 p24), p10 of Grapevine virus A, (GVA-p10), p14 of Grapevine virus B (GVB-p14), p10 of

Heracleum latent virus (HLV-p10), or p16 of Garlic common latent virus (GCLV-p16). Therefore, a suppressor of silencing, for example, but not limited to, HcPro, TEV-p1/HC-Pro, BYV-p21, TBSV p19, TCV-CP, CMV-2b, PVX-p25, PVM-p11, PVS-p11, BScV-p16, CTV-p23, GLRaV-2 p24, GBV-p14, HLV-p10, GCLV-p16 or GVA-p10, may be co-expressed along with the nucleic acid sequence encoding the protein of interest to further ensure high levels of protein production within a plant.

Furthermore, VLPs may be produced that comprise a combination of HA subtypes. For example, VLPs may comprise one or more than one HA from the subtype H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, H16, or a combination thereof. Selection of the combination of HAs may be determined by the intended use of the vaccine prepared from the VLP. For example a vaccine for use in inoculating birds may comprise any combination of HA subtypes, while VLPs useful for inoculating humans may comprise subtypes one or more than one of subtypes H1, H2, H3, H5. However, other HA subtype combinations may be prepared depending upon the use of the VLP. In order to produce VLPs comprising combinations of HA subtypes, the desired HA subtype may be co-expressed within the same cell, for example a plant cell.

Furthermore, VLPs produced as described herein do not comprise neuraminidase (NA). However, NA may be co-expressed with HA should VLPs comprising HA and NA be desired.

Therefore, the present invention further includes a suitable vector comprising the chimeric construct suitable for use with either stable or transient expression systems. The genetic information may be also provided within one or more than one construct. For example, a nucleotide sequence encoding a protein of interest may be introduced in one construct, and a second nucleotide sequence encoding a protein that modifies glycosylation of the protein of interest may be introduced using a separate construct. These nucleotide sequences may then be co-expressed within a plant. However, a construct comprising a nucleotide sequence encoding both the protein of interest and the protein that modifies glycosylation profile of the protein of interest may also be used. In this case the nucleotide sequence would comprise a first sequence comprising a first nucleic acid sequence encoding the protein of interest operatively linked to a promoter or regulatory region, and a second sequence comprising a second nucleic acid sequence encoding the protein that modifies the glycosylation profile of the protein of interest, the second sequence operatively linked to a promoter or regulatory region.

By "co-expressed" it is meant that two, or more than two, nucleotide sequences are expressed at about the same time within the plant, and within the same tissue of the plant. However, the nucleotide sequences need not be expressed at exactly the same time. Rather, the two or more nucleotide sequences are expressed in a manner such that the encoded products have a chance to interact. For example, the protein that modifies glycosylation of the protein of interest may be expressed either before or during the period when the protein of interest is expressed so that modification of the glycosylation of the protein of interest takes place. The two or more than two nucleotide sequences can be co-expressed using a transient expression system, where the two or more sequences are introduced within the plant at about the same time under conditions that both sequences are expressed. Alternatively, a platform plant comprising one of the nucleotide sequences, for example the sequence encoding the protein that modifies the glycosylation profile of the protein

of interest, may be transformed, either transiently or in a stable manner, with an additional sequence encoding the protein of interest. In this case, the sequence encoding the protein that modifies the glycosylation profile of the protein of interest may be expressed within a desired tissue, during a desired stage of development, or its expression may be induced using an inducible promoter, and the additional sequence encoding the protein of interest may be expressed under similar conditions and in the same tissue, to ensure that the nucleotide sequences are co-expressed.

The constructs of the present invention can be introduced into plant cells using Ti plasmids, Ri plasmids, plant virus vectors, direct DNA transformation, micro-injection, electroporation, etc. For reviews of such techniques see for example Weissbach and Weissbach, *Methods for Plant Molecular Biology*, Academy Press, New York VIII, pp. 421-463 (1988); Geierman and Corey, *Plant Molecular Biology*, 2d Ed. (1988); and Miki and Iyer, *Fundamentals of Gene Transfer in Plants*. In *Plant Metabolism*, 2d Ed. D T. Dennis, D H Turpin, D D Lefebvre, D B Layzell (eds), Addison Wesley, Langmans Ltd. London, pp. 561-579 (1997). Other methods include direct DNA uptake, the use of liposomes, electroporation, for example using protoplasts, micro-injection, microprojectiles or whiskers, and vacuum infiltration. See, for example, Bilanz, et al. (*Gene* 100: 247-250 (1991), Scheid et al. (*Mol. Gen. Genet.* 228: 104-112, 1991), Guerche et al. (*Plant Science* 52: 111-116, 1987), Neuhauser et al. (*Theor. Appl Genet.* 75: 30-36, 1987), Klein et al., *Nature* 327: 70-73 (1987); Howell et al. (*Science* 208: 1265, 1980), Horsch et al. (*Science* 227: 1229-1231, 1985), DeBlock et al., *Plant Physiology* 91: 694-701, 1989), *Methods for Plant Molecular Biology* (Weissbach and Weissbach, eds., Academic Press Inc., 1988), *Methods in Plant Molecular Biology* (Schuler and Zielinski, eds., Academic Press Inc., 1989), Liu and Lomonosoff (*J. Virol Meth.* 105:343-348, 2002.), U.S. Pat. Nos. 4,945,050; 5,036,006; and 5,100,792, U.S. patent application Ser. No. 08/438,666, filed May 10, 1995, and Ser. No. 07/951,715, filed Sep. 25, 1992, (all of which are hereby incorporated by reference).

Transient expression methods may be used to express the constructs of the present invention (see Liu and Lomonosoff, 2002, *Journal of Virological Methods*, 105:343-348; which is incorporated herein by reference). Alternatively, a vacuum-based transient expression method, as described by Kapila et al. 1997 (incorporated herein by reference) may be used. These methods may include, for example, but are not limited to, a method of Agro-inoculation or Agro-infiltration, however, other transient methods may also be used as noted above. With either Agro-inoculation or Agro-infiltration, a mixture of *Agrobacterium* comprising the desired nucleic acid enter the intercellular spaces of a tissue, for example the leaves, aerial portion of the plant (including stem, leaves and flower), other portion of the plant (stem, root, flower), or the whole plant. After crossing the epidermis the *Agrobacterium* infect and transfer t-DNA copies into the cells. The t-DNA is episomally transcribed and the mRNA translated, leading to the production of the protein of interest in infected cells, however, the passage of t-DNA inside the nucleus is transient.

If the nucleotide sequence of interest encodes a product that is directly or indirectly toxic to the plant, then by using the method of the present invention, such toxicity may be reduced throughout the plant by selectively expressing the nucleotide sequence of interest within a desired tissue or at a desired stage of plant development. In addition, the limited period of expression resulting from transient expression may

reduce the effect when producing a toxic product in the plant. An inducible promoter, a tissue-specific promoter, or a cell specific promoter, may be used to selectively direct expression of the sequence of interest.

The recombinant HA VLPs of the present invention can be used in conjunction with existing influenza vaccines, to supplement the vaccines, render them more efficacious, and to reduce the administration dosages necessary. As would be known to a person of skill in the art, the vaccine may be directed against one or more than one influenza virus. Examples of suitable vaccines include, but are not limited to those commercially available from Sanofi-Pasteur, ID Biomedical, Merial, Sinovac, Chiron, Roche, MedImmune, GlaxoSmithKline, Novartis, Sanofi-Aventis, Serono, Shire Pharmaceuticals and the like.

If desired, the VLPs of the present invention may be admixed with a suitable adjuvant as would be known to one of skill in the art. Furthermore, the VLP may be used in a vaccine composition comprising an effective dose of the VLP for the treatment of a target organism, as defined above. Furthermore, the VLP produced according to the present invention may be combined with VLPs obtained using different influenza proteins, for example, neuraminidase (NA).

Therefore, the present invention provides a method for inducing immunity to influenza virus infection in an animal or target organism comprising administering an effective dose of a vaccine comprising one or more than one VLP. The vaccine may be administered orally, intradermally, intranasally, intramuscularly, intraperitoneally, intravenously, or subcutaneously.

Administration of VLPs produced according to the present invention is described in Example 6. Administration of plant-made H5 VLP resulted in a significantly higher response when compared to administration of soluble HA (see FIGS. 21A and 21B).

As shown in FIGS. 26A and 26 B a subject administered A/Indonesia/5/05 H5 VLPs provided cross-protection to a challenge with influenza A/Turkey/582/06 (H5N1; "Turkey H5N1"). Administration of Indonesia H5 VLPs before challenge did not result in any loss of body mass. However in subject not administered H5VLPs, but challenged with Turkey H5N1, exhibited significant loss of body mass, and several subject died.

These data, therefore, demonstrate that plant-made influenza VLPs comprising the H5 hemagglutinin viral protein induce an immune response specific for pathogenic influenza strains, and that virus-like particles may bud from a plant plasma membrane.

Therefore, the present invention provides a composition comprising an effective dose of a VLP comprising an influenza virus HA protein, one or more than one plant lipid, and a pharmaceutically acceptable carrier. The influenza virus HA protein may be H5 Indonesia/5/2006. Also provided is a method of inducing immunity to an influenza virus infection in a subject. The method comprising administering the virus like particle comprising an influenza virus HA protein, one or more than one plant lipid, and a pharmaceutically acceptable carrier. The virus like particle may be administered to a subject orally, intradermally, intranasally, intramuscularly, intraperitoneally, intravenously, or subcutaneously.

Compositions according to various embodiments of the invention may comprise VLPs of two or more influenza strains or subtypes. "Two or more" refers to two, three, four, five, six, seven, eight, nine, 10 or more strains or subtypes. The strains or subtypes represented may be of a single

subtype (e.g. all H1N1, or all H5N1), or may be a combination of subtypes. Exemplary subtype and strains include, but are not limited to, those disclosed herein (e.g. A/New Caledonia/20/99 (H1N1), A/Indonesia/5/2006 (H5N1), A/chicken/New York/1995, A/herring gull/DE/677/88 (H2N8), A/Texas/32/2003, A/mallard/MN/33/00, A/duck/Shanghai/1/2000, A/northern pintail/TX/828189/02, A/Turkey/Ontario/6118/68(H8N4), A/shoveler/Iran/G54/03, A/chicken/Germany/N/1949(H10N7), A/duck/England/56 (H11N6), A/duck/Alberta/60/76(H12N5), A/Gull/Maryland/704/77(H13N6), A/Mallard/Gurjev/263/82, A/duck/Australia/341/83 (H15N8), A/black-headed gull/Sweden/5/99 (H16N3), B/Lee/40, C/Johannesburg/66, A/PuertoRico/8/34 (H1N1), A/Brisbane/59/2007 (H1N1), A/Solomon Islands 3/2006 (H1N1), A/Brisbane 10/2007 (H3N2), A/Wisconsin/67/2005 (H3N2), B/Malaysia/2506/2004, B/Florida/4/2006, A/Singapore/1/57 (H2N2), A/Anhui/1/2005 (H5N1), A/Vietnam/1194/2004 (H5N1), A/Teal/HongKong/W312/97 (H6N1), A/Equine/Prague/56 (H7N7), A/HongKong/1073/99 (H9N2)).

The choice of combination of strains and subtypes may depend on the geographical area of the subjects likely to be exposed to influenza, proximity of animal species to a human population to be immunized (e.g. species of waterfowl, agricultural animals such as swine, etc) and the strains they carry, are exposed to or are likely to be exposed to, predictions of antigenic drift within subtypes or strains, or combinations of these factors. Examples of combinations used in past years are available. Some or all of these strains may be employed in the combinations shown, or in other combinations, in the production of a vaccine composition.

More particularly, exemplary combinations may include VLPs from two or more strains or subtypes selected from the group comprising: A/Brisbane/59/2007 (H1N1), an A/Brisbane/59/2007 (H1N1)-like virus, A/Brisbane/10/2007 (H3N2), an A/Brisbane/10/2007 (H3N2)-like virus, B/Florida/4/2006 or an B/Florida/4/2006-like virus.

Another exemplary combination may include VLPs from two or more strains or subtypes selected from the group comprising A/Indonesia/5/2005, an A/Indonesia/5/2005-like virus, A/Vietnam/1194/2004, an A/Vietnam/1194/2004-like virus, A/Anhui/1/05, an A/Anhui/1/05-like virus, A/goose/Guizhou/337/2006, A/goose/Guizhou/337/2006-like virus, A/chicken/Shanxi/2/2006, or A/chicken/Shanxi/2/2006-like virus.

Another exemplary combination may include VLPs of A/Chicken/Italy/13474/99 (H7 type) or A/Chicken/British Columbia/04 (H7N3) strains of influenza.

Another exemplary combination may include VLPs of A/Chicken/HongKong/G9/97 or A/HongKong/1073/99. Another exemplary combination may comprise VLPs of A/Solomon Islands/3/2006. Another exemplary combination may comprise VLPs of A/Brisbane/10/2007. Another exemplary combination may comprise VLPs of A/Wisconsin/67/2005. Another exemplary combination may comprise VLPs of the B/Malaysia/2506/2004, B/Florida/4/2006 or B/Brisbane/3/2007 strains or subtypes.

The two or more VLPs may be expressed individually, and the purified or semi-purified VLPs subsequently combined. Alternately, the VLPs may be co-expressed in the same host, for example a plant. The VLPs may be combined or produced in a desired ratio, for example about equivalent ratios, or may be combined in such a manner that one subtype or strain comprises the majority of the VLPs in the composition.

Therefore, the invention provides for compositions comprising VLPs of two or more strains or subtypes.

VLPs of enveloped viruses generally acquire their envelope from the membrane they bud through. Plant plasma membranes have a phytosterol complement that may have immunostimulatory effects. To investigate this possibility, plant-made H5 VLPs were administered to animals in the presence or absence of an adjuvant, and the HAI (hemagglutination inhibition antibody response) determined (FIGS. 22A, 22B). In the absence of an added adjuvant plant-made H5 VLPs demonstrate a significant HAI, indicative of a systemic immune response to administration of the antigen. Furthermore, the antibody isotype profiles of VLPs administered in the present or absence of adjuvant are similar (FIG. 23A).

Table 5 lists sequences provided in various embodiments of the invention.

TABLE 5

Sequence description for sequence identifiers.		
SEQ ID No	Sequence Description	In Disclosure
1	N terminal H1 fragment	FIG. 5a
2	C terminal H1 fragment	FIG. 5b
3	H5 coding sequence	FIG. 6
4	primer Plato-443c	FIG. 7a
5	primer SpHA(Ind)-Plasto.r	FIG. 7b
6	primer Plasto-SpHA(Ind).c	FIG. 7c
7	primer HA(Ind)-Sac.r	FIG. 7d
8	Sequence of the alfalfa plastocyanin-based expression cassette used for the expression of H1	FIG. 1
9	HA1 peptide sequence (A/New Caledonia/20/99)	FIG. 8a
10	HA5 peptide sequence (A/Indonesia/5/2006)	FIG. 8b
11	Influenza A Subtype H7 coding sequence (A/chicken/New York/1995)	FIG. 9
12	Influenza A Subtype H2 coding sequence (A/herring gull/DE/677/88 (H2N8))	FIG. 10a
13	Influenza A Subtype H3 coding sequence (A/Texas/32/2003)	FIG. 10b
14	Influenza A Subtype H4 coding sequence (A/mallard/MN/33/00)	FIG. 10c
15	Influenza A Subtype H5 coding sequence (A/duck/Shanghai/1/2000)	FIG. 10d
16	Influenza A Subtype H6 coding sequence (A/northern pintail/TX/828189/02)	FIG. 10e
17	Influenza A Subtype H8 coding sequence (A/Turkey/Ontario/6118/68(H8N4))	FIG. 10f
18	Influenza A Subtype H9 coding sequence (A/shoveler/Iran/G54/03)	FIG. 10g
19	Influenza A Subtype H10 coding sequence (A/chicken/Germany/N/1949 (H10N7))	FIG. 10h
20	Influenza A Subtype H11 coding sequence (A/duck/England/56(H11N6))	FIG. 10i
21	Influenza A Subtype H12 coding sequence (A/duck/Alberta/60/76(H12N5))	FIG. 10j
22	Influenza A Subtype H13 coding sequence (A/Gull/Maryland/704/77 (H13N6))	FIG. 10k
23	Influenza A Subtype H14 coding sequence (A/Mallard/Gurjev/263/82)	FIG. 10l
24	Influenza A Subtype H15 coding sequence (A/duck/Australia/341/83 (H15N8))	FIG. 10m
25	Influenza A Subtype H16 coding sequence (A/black-headed gull/Sweden/5/99(H16N3))	FIG. 10n
26	Influenza B HA coding sequence (B/Lee/40)	FIG. 10o
27	Influenza C HA coding sequence (C/Johannesburg/66)	FIG. 10p
28	Complete HAO H1 sequence	FIG. 5c
29	Primer Xmal-pPlas.c	FIG. 10q
30	Primer SacI-ATG-pPlas.r	FIG. 10r
31	Primer SacI-PlasTer.c	FIG. 10s
32	Primer EcoRI-PlasTer.r	FIG. 10t

TABLE 5-continued

Sequence description for sequence identifiers.		
SEQ ID No	Sequence Description	In Disclosure
33	A/New Caledonia/20/99 (H1N1) GenBank Accession No. AY289929	FIG. 16
34	M. Sativa protein disulfide isomerase GenBank Accession No. Z11499	FIG. 17
35	A./PuertoRico/8/34 (H1N1) GenBank Accession No. NC_002016.1	FIG. 18
36	Clone 774: DNA from DraIII to SacI comprising plastocyanin regulatory region operatively linked to sequence encoding HA of A/Brisbane/59/2007 (H1N1)	FIG. 28
37	Clone 775: DNA from DraIII to SacI comprising plastocyanin regulatory region operatively linked to sequence encoding HA of A/Solomon Islands 3/2006 (H1N1)	FIG. 29
38	Clone 776: DNA from DraIII to SacI comprising plastocyanin regulatory region operatively linked to sequence encoding HA of A/Brisbane 10/2007 (H3N2)	FIG. 30
39	Clone 777: DNA from DraIII to SacI comprising plastocyanin regulatory region operatively linked to sequence encoding HA of A/Wisconsin/67/2005 (H3N2)	FIG. 31
40	Clone 778: DNA from DraIII to SacI comprising plastocyanin regulatory region operatively linked to sequence encoding HA of B/Malaysia/2506/2004	FIG. 32
41	Clone 779: DNA from DraIII to SacI comprising plastocyanin regulatory region operatively linked to sequence encoding HA of B/Florida/4/2006	FIG. 33
42	Clone 780: DNA from DraIII to SacI comprising plastocyanin regulatory region operatively linked to sequence encoding HA of A/Singapore/1/57 (H2N2)	FIG. 34
43	Clone 781: DNA from DraIII to SacI comprising plastocyanin regulatory region operatively linked to sequence encoding HA of A/Anhui/1/2005 (H5N1)	FIG. 35
44	Clone 782: DNA from DraIII to SacI comprising plastocyanin regulatory region operatively linked to sequence encoding HA of A/Vietnam/1194/2004 (H5N1)	FIG. 36
45	Clone 783: DNA from DraIII to SacI comprising plastocyanin regulatory region operatively linked to sequence encoding HA of A/Teal/HongKong/W312/97 (H6N1)	FIG. 37
46	Clone 784: DNA from DraIII to SacI comprising plastocyanin regulatory region operatively linked to sequence encoding HA of A/Equine/Prague/56 (H7N7)	FIG. 38
47	Clone 785: DNA from DraIII to SacI comprising plastocyanin regulatory region operatively linked to sequence encoding HA of A/HongKong/1073/99 (H9N2)	FIG. 39
48	Clone 774 HA amino acid sequence A/Brisbane/59/2007 (H1N1)	FIG. 40A
49	Clone 775 HA amino acid sequence A/Solomon Islands 3/2006 (H1N1)	FIG. 40B
50	Clone 776 HA amino acid sequence A/Brisbane 10/2007 (H3N2)	FIG. 41A
51	Clone 777 HA amino acid sequence A/Wisconsin/67/2005 (H3N2)	FIG. 41B
52	Clone 778 HA amino acid sequence B/Malaysia/2506/2004	FIG. 42A
53	Clone 779 HA amino acid sequence B/Florida/4/2006	FIG. 42B
54	Clone 780 HA amino acid sequence A/Singapore/1/57 (H2N2)	FIG. 43A

TABLE 5-continued

Sequence description for sequence identifiers.		
SEQ ID No	Sequence Description	In Disclosure
55	Clone 781 HA amino acid sequence A/Anhui/1/2005 (H5N1)	FIG. 43B
56	Clone 782 HA amino acid sequence A/Vietnam/1194/2004 (H5N1)	FIG. 44A
57	Clone 783 HA amino acid sequence A/Teal/HongKong/W312/97 (H6N1)	FIG. 44B
58	Clone 784 HA amino acid sequence A/Equine/Prague/56 (H7N7)	FIG. 45A
59	Clone 785 HA amino acid sequence A/HongKong/1073/99 (H9N2)	FIG. 45B
60	HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H5 from A/Indonesia/5/2005 (Construct # 660), alfalfa plastocyanin 3' UTR and terminator sequences	FIG. 51
61	HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H1 from A/New Caledonia/20/1999 (Construct # 540), alfalfa plastocyanin 3' UTR and terminator sequences	FIG. 52
62	HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H1 from A/Brisbane/59/2007 (construct #774), alfalfa plastocyanin 3' UTR and terminator sequences	FIG. 53
63	HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H1 from A/Solomon Islands/3/2006 (H1N1) (construct #775), alfalfa plastocyanin 3' UTR and terminator sequences	FIG. 54
64	HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H2 from A/Singapore/1/57 (H2N2) (construct # 780), alfalfa plastocyanin 3' UTR and terminator sequences	FIG. 55
65	HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H5 from A/Anhui/1/2005 (H5N1) (Construct # 781), alfalfa plastocyanin 3' UTR and terminator sequences	FIG. 56
66	HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H5 from A/Vietnam/1194/2004 (H5N1) (Construct # 782), alfalfa plastocyanin 3' UTR and terminator sequences	FIG. 57
67	HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H6 from A/Teal/Hong Kong/W312/97 (H6N1) (Construct # 783), alfalfa plastocyanin 3' UTR and terminator sequences	FIG. 58
68	HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H9 from A/Hong Kong/1073/99 (H9N2) (Construct # 785), alfalfa plastocyanin 3' UTR and terminator sequences	FIG. 59
69	HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H3 from A/Brisbane/10/2007 (H3N2), alfalfa plastocyanin 3' UTR and terminator sequences	FIG. 60
70	HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H3 from A/Wisconsin/67/2005 (H3N2), alfalfa	FIG. 61

TABLE 5-continued

Sequence description for sequence identifiers.		
SEQ ID No	Sequence Description	In Disclosure
	plastocyanin 3' UTR and terminator sequences	
71	HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of H7 from A/Equine/Prague/56 (H7N7), alfalfa plastocyanin 3' UTR and terminator sequences	FIG. 62
72	HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of HA from B/Malaysia/2506/2004, alfalfa plastocyanin 3' UTR and terminator sequences	prophetic FIG. 63
73	HA expression cassette comprising alfalfa plastocyanin promoter and 5' UTR, hemagglutinin coding sequence of HA from B/Florida/4/2006, alfalfa plastocyanin 3' UTR and terminator sequences	FIG. 64
74	Consensus of SEQ ID NO: 49, 48, 33 and 9	FIG. 65
75	Amino acid sequence of H1 New Caledonia (AAP34324.1) encoded by SEQ ID NO: 33	FIG. 67
76	Amino acid sequence of H1 Puerto Rico (NC_0409878.1) encoded by SEQ ID NO: 35	FIG. 68

The invention will now be described in detail by way of reference only to the following non-limiting examples. Methods and Materials

#### 1. Assembly of Expression Cassettes

All manipulations were done using the general molecular biology protocols of Sambrook and Russell (2001; which is incorporated herein by reference). The first cloning step consisted in assembling a receptor plasmid containing upstream and downstream regulatory elements of the alfalfa plastocyanin gene. The plastocyanin promoter and 5'UTR sequences were amplified from alfalfa genomic DNA using oligonucleotide primers XmaI-pPlas.c (SEQ ID NO: 29; FIG. 10Q) and SacI-ATG-pPlas.r (SEQ ID NO: 30; FIG. 10R). The resulting amplification product was digested with XmaI and SacI and ligated into pCAMBIA2300 (Cambia, Canberra, Australia), previously digested with the same enzymes, to create pCAMBIAPromo Plasto. Similarly, the 3'UTR sequences and terminator of the plastocyanin gene was amplified from alfalfa genomic DNA using the following primers: SacI-PlasTer.c (SEQ ID NO: 31; FIG. 10S) and EcoRI-PlasTer.r (SEQ ID NO: 32; FIG. 10T), and the product was digested with SacI and EcoRI before being inserted into the same sites of pCAMBIAPromoPlasto to create pCAMBIAPlasto.

The open reading frame from the H1 gene of influenza strain A/New Caledonia/20/99 (H1N1) was synthesized in two fragments (Plant Biotechnology Institute, National Research Council, Saskatoon, Canada). A first fragment synthesized corresponds to the wild-type H1 coding sequence (GenBank acc. No. AY289929; SEQ ID NO: 33; FIG. 16) lacking the signal peptide coding sequence at the 5' end and the transmembrane domain coding sequence at the 3' end. A BglII restriction site was added at the 5' end of the coding sequence and a dual SacI/StuI site was added immediately downstream of the stop codon at the 3' terminal end of the fragment, to yield SEQ ID NO: 1 (FIG. 5A). A second fragment encoding the C-terminal end of the H1 protein (comprising a transmembrane domain and cytoplas-

mic tail) from the KpnI site to the stop codon, and flanked in 3' by SacI and StuI restriction sites was also synthesized (SEQ ID NO. 2; FIG. 5B).

The first H1 fragment was digested with BglII and SacI and cloned into the same sites of a binary vector (pCAMBIAPlasto) containing the plastocyanin promoter and 5'UTR fused to the signal peptide of alfalfa protein disulfide isomerase (PDI) gene (nucleotides 32-103; Accession No. Z11499; SEQ ID NO: 34; FIG. 17) resulting in a PDI-H1 chimeric gene downstream of the plastocyanin regulatory elements. The sequence of the plastocyanin-based cassette containing the PDI signal peptide is presented in FIG. 1 (SEQ ID NO:8). The resulting plasmid contained H1 coding region fused to the PDI signal peptide and flanked by plastocyanin regulatory elements. The addition of the C-terminal end coding region (encoding the transmembrane domain and the cytoplasmic tail) was obtained by inserting the synthesized fragment (SEQ ID NO: 2; FIG. 5B) previously digested with KpnI and SacI, into the H1 expression plasmid. The resulting plasmid, named 540, is presented in FIG. 11 (also see FIG. 2A).

#### 2. Assembly of H5 Expression Cassette

A fragment encoding hemagglutinin from influenza strain A/Indonesia/5/05 (H5N1; Acc. No. LANL ISDN125873) was synthesized by Epoch Biolabs (Sugar Land, Tex., USA). The fragment produced, containing the complete H5 coding region including the native signal peptide flanked by a HindIII site immediately upstream of the initial ATG, and a SacI site immediately downstream of the stop (TAA) codon, is presented in SEQ ID NO: 3 (FIG. 6). The H5 coding region was cloned into a plastocyanin-based expression cassette by the PCR-based ligation method presented in Darveau et al. (1995). Briefly, a first PCR amplification was obtained using primers Plato-443c (SEQ ID NO: 4; FIG. 7A) and SpHA(Ind)-Plasto.r (SEQ ID NO:5; FIG. 7B) and pCAMBIA promoPlasto as template. In parallel, a second amplification was performed with primers Plasto-SpHA (Ind).c (SEQ ID NO: 6; FIG. 7C) and HA(Ind)-Sac.r (SEQ ID NO:7; FIG. 7D) with H5 coding fragment as template. The amplification obtained from both reactions were mixed together and the mixture served as template for a third reaction (assembling reaction) using Plato-443c (SEQ ID NO: 4; FIG. 7A) and HA(Ind)-Sac.r (SEQ ID NO: 7; FIG. 7D) as primers. The resulting fragment was digested with BamHI (in the plastocyanin promoter) and SacI (at the 3' end of the fragment) and cloned into pCAMBIAPlasto previously digested with the same enzymes. The resulting plasmid, named 660, is presented in FIG. 2B (also see FIG. 11).

The cassette encoding the soluble form of H1 was prepared by replacing the region coding for the transmembrane domain and the cytoplasmic tail in 540 by a fragment encoding the leucine zipper GCN4 pII variant (Harbury et al, 1993, Science 1993; 262: 1401-1407). This fragment was synthesized with flanking KpnI and SacI sites to facilitate cloning. The plasmid resulting from this replacement was named 544 and the expression cassette is illustrated in FIG. 11.

A fusion between the tobacco etch virus (TEV) 5'UTR and the open reading frame of the influenza A/PR/8/34 M1 gene (Acc. # NC\_002016) was synthesized with a flanking SacI site added downstream of the stop codon. The fragment was digested with SmaI (in the TEV 5'UTR) and SacI, and cloned into a 2X35S/TEV based expression cassette in a pCAMBIA binary plasmid. The resulting plasmid bore the M1 coding region under the control of a 2X355/TEV promoter and 5'UTR and the NOS terminator (construct 750; FIG. 11).

An HcPro construct (35HcPro) was prepared as described in Hamilton et al. (2002). All clones were sequenced to confirm the integrity of the constructs. The plasmids were used to transform *Agrobacterium tumefaciens* (AGL1; ATCC, Manassas, Va. 20108, USA) by electroporation (Mattanovich et al., 1989). The integrity of all *A. tumefaciens* strains were confirmed by restriction mapping.

### 3. Preparation of Plant Biomass, Inoculum, Agroinfiltration, and Harvesting

*Nicotiana benthamiana* or *Nicotiana tabacum* plants were grown from seeds in flats filled with a commercial peat moss substrate. The plants were allowed to grow in the greenhouse under a 16/8 photoperiod and a temperature regime of 25° C. day/20° C. night. Three weeks after seeding, individual plantlets were picked out, transplanted in pots and left to grow in the greenhouse for three additional weeks under the same environmental conditions. Prior to transformation, apical and axillary buds were removed at various times as indicated below, either by pinching the buds from the plant, or by chemically treating the plant

*Agrobacterium* transfected with constructs 660, 540, 544, 750 or 35SHcPro were grown in a YEB medium supplemented with 10 mM 2-[N-morpholino]ethanesulfonic acid (MES), 20 μM acetosyringone, 50 μg/ml kanamycin and 25 μg/ml of carbenicillin pH5.6 until they reached an OD<sub>600</sub> between 0.6 and 1.6. *Agrobacterium* suspensions were centrifuged before use and resuspended in infiltration medium (10 mM MgCl<sub>2</sub> and 10 mM MES pH 5.6). Syringe-infiltration was performed as described by Liu and Lomonosoff (2002, *Journal of Virological Methods*, 105:343-348). For vacuum-infiltration, *A. tumefaciens* suspensions were centrifuged, resuspended in the infiltration medium and stored overnight at 4° C. On the day of infiltration, culture batches were diluted in 2.5 culture volumes and allowed to warm before use. Whole plants of *N. benthamiana* or *N. tabacum* were placed upside down in the bacterial suspension in an air-tight stainless steel tank under a vacuum of 20-40 Torr for 2-min. Following syringe or vacuum infiltration, plants were returned to the greenhouse for a 4-5 day incubation period until harvest.

### 4. Leaf Sampling and Total Protein Extraction

Following incubation, the aerial part of plants was harvested, frozen at -80° C., crushed into pieces. Total soluble proteins were extracted by homogenizing (Polytron) each sample of frozen-crushed plant material in 3 volumes of cold 50 mM Tris pH 7.4, 0.15 M NaCl, and 1 mM phenylmethanesulfonyl fluoride. After homogenization, the slurries were centrifuged at 20,000 g for 20 min at 4° C. and these clarified crude extracts (supernatant) kept for analyses. The total protein content of clarified crude extracts was deter-

mined by the Bradford assay (Bio-Rad, Hercules, Calif.) using bovine serum albumin as the reference standard.

### 5. Size Exclusion Chromatography of Protein Extract

Size exclusion chromatography (SEC) columns of 32 ml Sephacryl™ S-500 high resolution beads (S-500 HR: GE Healthcare, Uppsala, Sweden, Cat. No. 17-0613-10) were packed and equilibrated with equilibration/elution buffer (50 mM Tris pH8, 150 mM NaCl). One and a half milliliter of crude protein extract was loaded onto the column followed by an elution step with 45 mL of equilibration/elution buffer. The elution was collected in fractions of 1.5 mL relative protein content of eluted fractions was monitored by mixing 10 μL of the fraction with 200 μL of diluted Bio-Rad protein dye reagent (Bio-Rad, Hercules, Calif. The column was washed with 2 column volumes of 0.2N NaOH followed by 10 column volumes of 50 mM Tris pH8, 150 mM NaCl, 20% ethanol. Each separation was followed by a calibration of the column with Blue Dextran 2000 (GE Healthcare Bio-Science Corp., Piscataway, N.J., USA). Elution profiles of Blue Dextran 2000 and host soluble proteins were compared between each separation to ensure uniformity of the elution profiles between the columns used.

### 6. Protein Analysis and Immunoblotting

Protein concentrations were determined by the BCA protein assay (Pierce Biochemicals, Rockport Ill.). Proteins were separated by SDS-PAGE under reducing conditions and stained with Coomassie Blue. Stained gels were scanned and densitometry analysis performed using ImageJ Software (NIH).

Proteins from elution fraction from SEC were precipitated with acetone (Bollag et al., 1996), resuspended in 1/5 volume in equilibration/elution buffer and separated by SDS-PAGE under reducing conditions and electrotransferred onto polyvinylene difluoride (PVDF) membranes (Roche Diagnostics Corporation, Indianapolis, Ind.) for immunodetection. Prior to immunoblotting, the membranes were blocked with 5% skim milk and 0.1% TWEEN-20 non-ionic detergent (Sigma-Aldrich Corporation, St. Louis, Mo.) in Tris-buffered saline (TBS-T) for 16-18 h at 4° C.

Immunoblotting was performed by incubation with a suitable antibody (Table 6), in 2 μg/ml in 2% skim milk in TBS-TWEEN-20 non-ionic detergent (Sigma-Aldrich Corporation, St. Louis, Mo.) 0.1%. Secondary antibodies used for chemiluminescence detection were as indicated in Table 4, diluted as indicated in 2% skim milk in TBS-TWEEN-20 non-ionic detergent (Sigma-Aldrich Corporation, St. Louis, Mo.) 0.1%. Immunoreactive complexes were detected by chemiluminescence using luminol as the substrate (Roche Diagnostics Corporation). Horseradish peroxidase-enzyme conjugation of human IgG antibody was carried out by using the EZ-Link Plus® Activated Peroxidase conjugation kit (Pierce, Rockford, Ill.).

TABLE 6

Electrophoresis conditions, antibodies, and dilutions for immunoblotting of expressed proteins.						
HA	Influenza strain	Electrophoresis condition	Primary antibody	Dilution	Secondary antibody	Dilution
H1	A/Brisbane/59/2007 (H1N1)	Reducing	FII 10-150	4 μg/ml	Goat anti-mouse (JIR 115-035-146)	1:10000
H1	A/Solomon Islands/3/2006 (H1N1)	Reducing	NIBSC 07/104	1:2000	Rabbit anti-sheep (JIR 313-035-045)	1:10000

TABLE 6-continued

Electrophoresis conditions, antibodies, and dilutions for immunoblotting of expressed proteins.						
HA	Influenza strain	Electrophoresis condition	Primary antibody	Dilution	Secondary antibody	Dilution
H1	A/New Caledonia/20/99 (H1N1)	Reducing	FII 10-I50	4 µg/ml	Goat anti-mouse (JIR 115-035-146)	1:10000
H2	A/Singapore/1/57 (H2N2)	Non-reducing	NIBSC 00/440	1:1000	Rabbit anti-sheep (JIR 313-035-045)	1:10000
H5	A/Indonesia/5/2005 (H5N1)	Reducing	ITC IT-003-005V	1:4000	Goat anti-rabbit (JIR 111-035-144)	1:10000
H5	A/Anhui/1/2005 (H5N1)	Reducing	NIBSC 07/338	1:750	Rabbit anti-sheep (JIR 313-035-045)	1:10000
H5	A/Vietnam/1194/2004 (H5N1)	Non-reducing	ITC IT-003-005	1:2000	Goat anti-rabbit (JIR 111-035-144)	1:10000
H6	A/Teal/Hong Kong/W312/97 (H6N1)	Non-reducing	BEI NR 663	1:500	Rabbit anti-sheep (JIR 313-035-045)	1:10000
H9	A/Hong Kong/1073/99 (H9N2)	Reducing	NIBSC 07/146	1:1000	Rabbit anti-sheep (JIR 313-035-045)	1:10000

HA: HA subtype;

FII: Fitzgerald Industries International, Concord, MA, USA;

NIBSC: National Institute for Biological Standards and Control;

JIR: Jackson ImmunoResearch, West Grove, PA, USA;

BEI NR: Biodefense and emerging infections research resources repository;

ITC: Immune Technology Corporation, Woodside, NY, USA;

Hemagglutination assay for H5 was based on a method described by Nayak and Reichl (2004). Briefly, serial double dilutions of the test samples (100 µL) were made in V-bottomed 96-well microtiter plates containing 100 µL PBS, leaving 100 µL of diluted sample per well. One hundred microliters of a 0.25% turkey red blood cells suspension (Bio Link Inc., Syracuse, N.Y.) were added to each well, and plates were incubated for 2 h at room temperature. The reciprocal of the highest dilution showing complete hemagglutination was recorded as HA activity. In parallel, a recombinant HA standard (A/Vietnam/1203/2004 H5N1) (Protein Science Corporation, Meriden, Conn.) was diluted in PBS and run as a control on each plate.

#### 7. Sucrose Gradient Ultracentrifugation

One milliliter of fractions 9, 10 and 11 eluted from the gel filtration chromatography on H5-containing biomass were pooled, loaded onto a 20-60% (w/v) discontinuous sucrose density gradient, and centrifuged 17.5 h at 125 000 g (4° C.). The gradient was fractionated in 19 3-mL fractions starting from the top, and dialyzed to remove sucrose prior to immunological analysis and hemagglutination assays.

#### 8. Electron Microscopy

Elution fractions from SEC to be observed by electron microscopy (EM) were first concentrated using 30 MWCO ultrafiltration units (Millipore, Billerica, Mass., USA). The concentrated fractions were fixed in PBS pH 7.4 containing 2% glutaraldehyde for 24 h at 4° C. Once fixed the samples were adsorbed onto Formvar-coated 200-mesh nickel grids

1% phosphotungstic acid. Observation was performed under transmission electron microscopy at magnifications ranging from 10,000× to 150,000× (for images in FIGS. 4A and 4B).

40 Alternately, one hundred microliters of the samples to be examined were placed in an Airfuge ultracentrifugation tube (Beckman Instruments, Palo Alto, Calif., USA). A grid was placed at the bottom of the tube which was then centrifuged 5 min at 120 000 g. The grid was removed, gently dried, and placed on a drop of 3% phosphotungstic acid at pH 6 for staining. Grids were examined on a Hitachi 7100 transmission electron microscope (TEM) (for images in FIGS. 14B, 15B and 15C).

50 For images in FIG. 19, leaf blocks of approximately 1 mm<sup>3</sup> were fixed in PBS containing 2.5% glutaraldehyde and washed in PBS containing 3% sucrose before a post-fixation step in 1.33% osmium tetroxide. Fixed samples were imbedded in Spurr resin and ultrathin layers were laid on a grid. Samples were positively stained with 5% uranyl acetate and 0.2% lead citrate before observation. Grids were examined on a Hitachi 7100 transmission electron microscope (TEM).

#### 9. Plasma Membrane Lipid Analysis

Plasma membranes (PM) were obtained from tobacco leaves and cultured BY2 cells after cell fractionation according to Mongrand et al. by partitioning in an aqueous polymer two-phase system with polyethylene glycol 3350/dextran T-500 (6.6% each). All steps were performed at 4° C.

65 Lipids were extracted and purified from the different fractions according to Bligh and Dyer. Polar and neutral lipids were separated by mono-dimensional HP-TLC using the solvent systems described in Lefebvre et al. Lipids of

PM fractions were detected after staining with copper acetate as described by Macala et al. Lipids were identified by comparison of their migration time with those of standards (all standards were obtained from Sigma-Aldrich, St-Louis, Mo., USA, except for SG which was obtained from Matreya, Pleasant Gap, Pa., USA).

#### 10. H5 VLP Purification

Frozen 660-infiltrated leaves of *N. benthamiana* were homogenized in 1.5 volumes of 50 mM Tris pH 8, NaCl 150 mM and 0.04% sodium meta-bisulfite using a commercial blender. The resulting extract was supplemented with 1 mM PMSF and adjusted to pH 6 with 1 M acetic acid before being heated at 42° C. for 5 min. Diatomaceous earth (DE) was added to the heat-treated extract to adsorb the contaminants precipitated by the pH shift and heat treatment, and the slurry was filtered through a Whatman paper filter. The resulting clarified extract was centrifuged at 10,000×g for 10 minutes at RT to remove residual DE, passed through 0.8/0.2 µm Acropack 20 filters and loaded onto a fetuin-agarose affinity column (Sigma-Aldrich, St-Louis, Mo., USA). Following a wash step in 400 mM NaCl, 25 mM Tris pH 6, bound proteins were eluted with 1.5 M NaCl, 50 mM MES pH 6. Eluted VLP were supplemented with TWEEN-80 non-ionic detergent (Sigma-Aldrich Corporation, St. Louis, Mo.) to a final concentration of 0.0005% (v/v). VLP were concentrated on a 100 kDa MWCO Amicon membrane, centrifuged at 10,000×g for 30 minutes at 4° C. and resuspended in PBS pH 7.4 with 0.01% TWEEN-80 non-ionic detergent (Sigma-Aldrich Corporation, St. Louis, Mo.) and 0.01% thimerosal. Suspended VLPs were filter-sterilized before use.

#### 11. Animal Studies

##### Mice

Studies on the immune response to influenza VLP administration were performed with 6-8 week old female BALB/c mice (Charles River Laboratories). Seventy mice were randomly divided into fourteen groups of five animals. Eight groups were used for intramuscular immunization and six groups were used to test intranasal route of administration. All groups were immunized in a two-dose regiment, the boost immunization being done 3 weeks following the first immunization.

For intramuscular administration in hind legs, unanaesthetized mice were immunized with either the plant-made VLP H5 vaccine (0.1, 1, 5 or 12 µg), or a control hemagglutinin (HA) antigen. The control HA comprised recombinant soluble hemagglutinin produced based on strain A/Indonesia/5/05 H5N1 and purified from 293 cell culture (Immune Technology Corp., New York, USA) (used at 5 µg per injection unless otherwise indicated). Buffer control was PBS. This antigen consists of amino acids 18-530 of the HA protein, and has a His-tag and a modified cleavage site. Electron microscopy confirmed that this commercial product is not in the form of VLPs.

To measure the effect of adjuvant, two groups of animals were immunized with 5 µg plant-made VLP H5 vaccine plus one volume Alhydrogel 2% (alum, Accurate Chemical & Scientific Corporation, Westbury, N.Y., US) or with 5 µg recombinant hemagglutinin purified from 293 cell culture plus 1 volume alum. Seventy mice were randomly divided into fourteen groups of five animals. Eight groups were used for intramuscular immunization and six groups were used to test intranasal route of administration. All groups were immunized according to a prime-boost regimen, the boost immunization performed 3 weeks following the first immunization.

For intramuscular administration in hind legs, unanaesthetized mice were immunized with the plant-made H5 VLP (0.1, 1, 5 or 12 µg), or the control hemagglutinin (HA) antigen (5 µg) or PBS. All antigen preparations were mixed with Alhydrogel 1% (alum, Accurate Chemical & Scientific Corporation, Westbury, N.Y., US) in a 1:1 volume ratio prior to immunizations. To measure the effect of adjuvant, two groups of animals were immunized with either 5 µg plant-made VLP H5 vaccine or with 5 µg of control HA antigen without any adjuvant.

For intranasal administration, mice were briefly anaesthetized by inhalation of isoflurane using an automated induction chamber. They were then immunized by addition of 4 µl drop/nostril with the plant-made VLP vaccine (0.1 or 1 µg), or with control HA antigen (1 µg) or with PBS. All antigen preparations were mixed with chitosan glutamate 1% (Protosan, Novamatrix/FMC BioPolymer, Norway) prior to immunizations. The mice then breathed in the solutions. To verify the effect of adjuvant with the intranasal route of administration, two groups of animals were immunized with 1 µg plant-made VLP H5 vaccine or with 1 µg control HA antigen.

##### Ferrets

Ten groups of 5 ferrets (male, 18-24 weeks old, mass of approx 1 kg) were used. Treatment for each group is as described in Table 7. The adjuvant used was Alhydrogel (alum) (Superfos Biosector, Denmark) 2% (final=1%). Vaccine composition was membrane-associated A/Indonesia/5/05 (H5N1) VLPs produced as described. The vaccine control (positive control) was a fully glycosylated membrane-bound recombinant H5 from Indonesia strain produced using adenovirus in 293 cell culture by Immune Technology Corporation (ITC).

TABLE 7

Treatment groups				
Group	n	Product injected to animals	Route of administration	Adjuvant
1	5	PBS (negative control)	i.m.*	—
2	5	Vaccine-plant, 1 µg	i.m.	—
3	5	Vaccine-plant, 1 µg	i.m.	Alum
4	5	Vaccine-plant, 5 µg	i.m.	—
5	5	Vaccine-plant, 5 µg	i.m.	Alum
6	5	Vaccine-plant, 7.5 µg	i.m.	—
7	5	Vaccine-plant, 15 µg	i.m.	—
8	5	Vaccine-plant, 15 µg	i.m.	Alum
9	5	Vaccine-plant, 30 µg	i.m.	—
10	5	Vaccine-control, 5 µg	i.m.	—

\* i.m.: intramuscular

Ferrets were assessed for overall health and appearance (body weight, rectal temperature, posture, fur, movement patterns, breathing, excrement) regularly during the study. Animals were immunized by intramuscular injection (0.5-1.0 total volume) in quadriceps at day 0, 14 and 28; for protocols incorporating adjuvant, the vaccine composition was combined with Alhydrogel immediately prior to immunization in a 1:1 volume ratio). Serum samples were obtained on day 0 before immunizing, and on day 21 and 35. Animals were sacrificed (exsanguination/cardiac puncture) on days 40-45, and, spleens were collected and necropsy performed.

Anti-influenza antibody titres may be quantified in ELISA assays using homologous or heterologous inactivated H5N1 viruses.

Hemagglutination inhibitory antibody titers of serum samples (pre-immune, day 21 and day 35) were evaluated by

microtiter HAI as described (Aymard et al 1973). Briefly, sera were pretreated with receptor-destroying enzyme, heat-inactivated and mixed with a suspension of erythrocytes (washed red blood cells-RBC). Horse washed RBC (10%) from Lampire are recommended and considering that the assay may vary depending of the source of the RBC (horse-dependant), washed RBCs from 10 horses have been tested to select the most sensitive batch. Alternately, turkey RBC may be used. Antibody titer was expressed as the reciprocal of the highest dilution which completely inhibits hemagglutination.

Cross-reactive HAI titers: HAI titers of ferrets immunized with a vaccine for the A/Indonesia/5/05 (clade 2.1) were measured using inactivated H5N1 influenza strains from another subclade or clade such as the clade 1 Vietnam strains A/Vietnam/1203/2004 and A/Vietnam/1194/2004 or the A/Anhui/01/2005 (subclade 2.3) or the A/turkey/Turkey/1/05 (subclade 2.2). All analyses were performed on individual samples.

Data analysis: Statistical analysis (ANOVA) will be performed on all data to establish if differences between groups are statistically significant.

#### Experimental Design for Lethal Challenge (Mice)

One hundred twenty eight mice were randomly divided into sixteen groups of eight animals, one group being unimmunized and not challenged (negative control). All groups were immunized via intramuscular administration in a two-dose regimen, the second immunization being done 2 weeks following the first immunization.

For intramuscular administration in hind legs, unanaesthetized mice were immunized with the plant-made H5 VLP (1, 5 or 15 µg), or 15 µg of control HA antigen or PBS. All antigen preparations were mixed with one volume of Alhydrogel 1% prior to immunizations (alum, Accurate Chemical & Scientific Corporation, Westbury, N.Y., US).

During the immunization period, mice were weighted once a week and observation and monitored for local reactions at the injection site.

Twenty two days following the second immunization, anesthetized mice were challenged intranasally (i.n.) into a BL4 containment laboratory (P4-Jean Mérieux-INSERM, Lyon, France) with  $4.09 \times 10^6$  50% cell culture infective dose (CCID50) of influenza A/Turkey/582/06 virus (kindly provided by Dr. Bruno Lina, Lyon University, Lyon, France). Following challenge, mice were observed for ill clinical symptoms and weighed daily, over a fourteen day period. Mice with severe infection symptoms and weight loss of  $\geq 25\%$  were euthanized after anaesthesia.

Blood Collection, Lung and Nasal Washes and Spleen Collection

Lateral saphenous vein blood collection was performed fourteen days after the first immunization and fourteen days after second immunization on unanaesthetized animal Serum was collected by centrifuging at 8000 g for 10 min.

Four weeks after second immunisation, mice were anaesthetized with CO<sub>2</sub> gas and immediately upon termination, cardiac puncture was used to collect blood.

After final bleeding, a catheter was inserted into the trachea towards the lungs and one ml of cold PBS-protease inhibitor cocktail solution was put into a 1 cc syringe attached to the catheter and injected into the lungs and then removed for analysis. This wash procedure was performed two times. The lung washes were centrifuged to remove cellular debris. For nasal washes, a catheter was inserted towards the nasal area and 0.5 ml of the PBS-protease inhibitor cocktail solution was pushed through the catheter into the nasal passages and then collected. The nasal washes

were centrifuged to remove cellular debris. Spleen collection was performed on mice immunized intramuscularly with 5 µg of adjuvanted plant-made vaccine or 5 µg adjuvanted recombinant H5 antigen as well as on mice immunized intranasally with 1 µg of adjuvanted plant-made vaccine or 1 µg adjuvanted recombinant H5 antigen. Collected spleens were placed in RPMI supplemented with gentamycin and mashed in a 50 ml conical tube with plunger from a 10 ml syringe. Mashed spleens were rinsed 2 times and centrifuged at 2000 rpm for 5 min and resuspended in ACK lysing buffer for 5 min at room temperature. The splenocytes were washed in PBS-gentamycin, resuspended in 5% RPMI and counted. Splenocytes were used for proliferation assay. Antibody Titers

Anti-influenza antibody titers of sera were measured at 14 days after the first immunization as well as 14 and 28 days after the second immunisation. The titer were determined by enzyme-linked immunosorbent assay (ELISA) using the inactivated virus A/Indonesia/5/05 as the coating antigen. The end-point titers were expressed as the reciprocal value of the highest dilution that reached an OD value of at least 0.1 higher than that of negative control samples.

For antibody class determination (IgG1, IgG2a, IgG2b, IgG3, IgM), the titers were evaluated by ELISA as previously described.

#### Hemagglutination Inhibition (HI) Titers

Hemagglutination inhibition (HI) titers of sera were measured at 14 and 28 days after the second immunisation as previously described (WHO 2002; Kendal 1982). Inactivated virus preparations from strains A/Indonesia/5/05 or A/Vietnam/1203/2004 were used to test mouse serum samples for HI activity. Sera were pre-treated with receptor-destroying enzyme II (RDE II) (Denka Seiken Co., Tokyo, Japan) prepared from *Vibrio cholerae* (Kendal 1982). HI assays were performed with 0.5% turkey red blood cells. HI antibody titres were defined as the reciprocal of the highest dilution causing complete inhibition of agglutination.

## EXAMPLES

### Example 1

#### Transient Expression of Influenza Virus A/Indonesia/5/05 (H5N1) Hemagglutinin by Agroinfiltration in *N. benthamiana* Plants

The ability of the transient expression system to produce influenza hemagglutinin was determined through the expression of the H5 subtype from strain A/Indonesia/5/05 (H5N1). As presented in FIG. 11, the hemagglutinin gene coding sequence (Acc. # EF541394), with its native signal peptide and transmembrane domain, was first assembled in the plastocyanin expression cassette—promoter, 5'UTR, 3'UTR and transcription termination sequences from the alfalfa plastocyanin gene—and the assembled cassette (660) was inserted into to a pCAMBIA binary plasmid. This plasmid was then transfected into *Agrobacterium* (AGL1), creating the recombinant strain AGL1/660, which was used for transient expression.

*N. benthamiana* plants were infiltrated with AGL1/660, and the leaves were harvested after a six-day incubation period. To determine whether H5 accumulated in the agroinfiltrated leaves, protein were first extracted from infiltrated leaf tissue and analyzed by Western blotting using anti-H5 (Vietnam) polyclonal antibodies. A unique band of approximately 72 kDa was detected in extracts (FIG. 12), corresponding in size to the uncleaved HAO form of influenza

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hemagglutinin. The commercial H5 used as positive control (A/Vietnam/1203/2004; Protein Science Corp., Meriden, Conn., USA) was detected as two bands of approximately 48 and 28 kDa, corresponding to the molecular weight of HA1 and HA2 fragments, respectively. This demonstrated that expression of H5 in infiltrated leaves results in the accumulation of the uncleaved translation product.

The formation of active HA trimers was demonstrated by the capacity of crude protein extracts from AGL1/660-transformed leaves to agglutinate turkey red blood cells (data not shown).

#### Example 2

##### Characterization of Hemagglutinin-Containing Structures in Plant Extracts Using Size Exclusion Chromatography

The assembly of plant-produced influenza hemagglutinin into high molecular weight structures was assessed by gel filtration. Crude protein extracts from AGL1/660-infiltrated plants (1.5 mL) were fractionated by size exclusion chromatography (SEC) on Sephacryl™ S-500 HR columns (GE Healthcare Bio-Science Corp., Piscataway, N.J., USA). Elution fractions were assayed for their total protein content and for HA abundance using immunodetection with anti-HA antibodies (FIG. 13A). As shown in FIG. 13A, Blue Dextran (2 MDa) elution peaked early in fraction 10 while the bulk of host proteins was retained in the column and eluted between fractions 14 and 22. When proteins from 200 μL of each SEC elution fraction were concentrated (5-fold) by acetone-precipitation and analyzed by Western blotting (FIG. 15A, H5), hemagglutinin (H5) was primarily found in fractions 9 to 14 (FIG. 13B). Without wishing to be bound by theory, this suggests that the HA protein had either assembled into a large superstructure or that it has attached to a high molecular weight structure.

A second expression cassette was assembled with the H1 nucleic acid sequence from A/New Caledonia/20/99 (H1N1) (SEQ ID NO: 33; FIG. 16; GenBank Accession No. AY289929) to produce construct 540 (FIG. 11). A chimeric gene construct was designed so as to produce a soluble trimeric form of H1 in which the signal peptide originated from a plant protein disulfide isomerase gene, and the transmembrane domain of H1 was replaced by the pII variant of the GCN4 leucine zipper, a peptide shown to self-assemble into trimers (Harbury et al., 1993) (cassette 544, FIG. 11). Although lacking the transmembrane domain, this soluble trimeric form was capable of hemagglutination (data not shown).

Protein extracts from plants infiltrated with AGL1/540 or AGL1/544 were fractionated by SEC and the presence of H1 eluted fractions was examined by Western blotting with anti-influenza A antibodies (Fitzgerald, Concord, Mass., USA). In AGL1/540-infiltrated leaves, H1 accumulated mainly as a very high molecular weight structure, with the peak was skewed toward smaller size structures (H1; FIG. 13C). In AGL1/544-infiltrated leaves, the soluble form of H1 accumulated as isolated trimers as demonstrated by the elution pattern from gel filtration which parallels the host protein elution profile (soluble H1; FIG. 13D). In comparison, H1 rosettes (Protein Science Corp., Meriden, Conn., USA), consisting in micelles of 5-6 trimers of hemagglutinin eluted at fractions 12 to 16 (FIG. 13E), earlier than the soluble form of H1 (FIG. 13D) and later than the native H1 (FIG. 13C).

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To evaluate the impact of M1 co-expression on hemagglutinin assembly into structure, a M1 expression cassette was assembled using the nucleic acid corresponding to the coding sequence of the A/PR/8/34 (H1N1) M1 (SEQ ID NO: 35; FIG. 18; GenBank Accession No. NC\_002016). The construct was named 750 and is presented in FIG. 11. For the co-expression of M1 and H1, suspensions of AGL1/540 and AGL1/750 were mixed in equal volume before infiltration. Co-infiltration of multiple *Agrobacterium* suspensions permits co-expression of multiple transgenes. The Western blot analysis of SEC elution fractions shows that the co-expression of M1 did not modify the elution profile of the H1 structures, but resulted in a decrease in H1 accumulation in the agroinfiltrated leaves (see FIG. 13F).

#### Example 3

##### Isolation of H5 Structures by Centrifugation in Sucrose Gradient and Observation Under Electron Microscopy

The observation of hemagglutinin structure under electron microscopy (EM) required a higher concentration and purity level than that obtained from SEC on crude leaf protein extracts. To allow EM observation of H5 structures, a crude leaf protein extract was first concentrated by PEG precipitation (20% PEG) followed by resuspension in 1/10 volumes of extraction buffer. The concentrated protein extract was fractionated by S-500 HR gel filtration and elution fractions 9, 10, and 11 (corresponding to the void volume of the column) were pooled and further isolated from host proteins by ultracentrifugation on a 20-60% sucrose density gradient. The sucrose gradient was fractionated starting from the top and the fractions were dialysed and concentrated on a 100 NMWL centrifugal filter unit prior to analysis. As shown on the Western blots and hemagglutination results (FIG. 14A), H5 accumulated mainly in fractions 16 to 19 which contained ≈60% sucrose, whereas most of the host proteins peaked at fraction 13. Fractions 17, 18, and 19 were pooled, negatively stained, and observed under EM. Examination of the sample clearly demonstrated the presence of spiked spheric structures ranging in size from 80 to 300 nm which matched the morphological characteristics of influenza VLPs (FIG. 14B).

#### Example 4

##### Purification of Influenza H5 VLPs from Plant Biomass

In addition to an abundant content of soluble proteins, plant leaf extracts contain a complex mixture of soluble sugars, nucleic acids and lipids. The crude extract was clarified by a pH shift and heat treatment followed by filtration on diatomaceous earth (see Material and method section for a detailed description of the clarification method). FIG. 15A (lanes 1-4) presents a Coomassie Blue stained gel comparing protein content at the various steps of clarification. A comparison of protein content in the crude extract (lane 1) and in the clarified extract (lane 4) reveals the capacity of the clarification steps to reduce the global protein content and remove most of the major contaminant visible at 50 kDa in crude leaf extracts. The 50 kDa band corresponds to the RuBisCO large subunit, representing up to 30% of total leaf proteins.

Influenza H5 VLPs were purified from these clarified extracts by affinity chromatography on a fetuin column. A

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comparison of the load fraction (FIG. 15A, lane 5) with the flowthrough (FIG. 15A, lane 6) and the eluted VLPs (FIG. 15A, lane 7) demonstrates the specificity of the fetuin affinity column for influenza H5 VLPs in plant clarified extract.

The purification procedure resulted in over 75% purity in H5, as determined by densitometry on the Coomassie Blue stained SDS-PAGE gel (FIG. 15A, lane 7). In order to assess the structural quality of the purified product, the purified H5 was concentrated on a 100 NMWL (nominal molecular weight limit) centrifugal filter unit and examined under EM after negative staining FIG. 15B shows a representative sector showing the presence of profuse VLPs. A closer examination confirmed the presence of spikes on the VLPs (FIG. 15C).

As shown in FIG. 15D, H5 VLPs were purified to approx. 89% purity from clarified leaf extract by affinity chromatography on a fetuin column, based on the density of the Coomassie Blue stained H5 hemagglutinin and on total protein content determination by the BCA method.

The bioactivity of HA VLPs was confirmed by their capacity to agglutinate turkey red blood cells (data not shown).

FIG. 20B also confirms the identity of the purified VLP visualized by Western blotting and immunodetection with an anti-H5 polyclonal serum (A/Vietnam/1203/2004). A unique band of approximately 72 kDa is detected and corresponds in size to the uncleaved HA0 form of influenza hemagglutinin. FIG. 15c shows the VLP structure of the vaccine with the hemagglutinin spikes covering its structure.

VLPs were formulated for immunization of mice by filtering through a 0.22  $\mu\text{m}$  filter; endotoxin content was measured using the endotoxin LAL (*Limulus Amebocyte Lysate*) detection kit (Lonza, Walkersville, Miss., USA). The filtered vaccine contained  $105.8 \pm 11.6\%$  EU/ml (endotoxin units/ml).

## Example 5

## Localization of Influenza VLPs in Plants

To localize the VLPs and confirm their plasma membrane origin, thin leaf sections of H5-producing plants were fixed and examined under TEM after positive staining. Observation of leaf cells indicated the presence of VLPs in extracellular cavities formed by the invagination of the plasma membrane (FIG. 19). The shape and position of the VLPs observed demonstrated that despite the apposition of their plasma membranes on the cell wall, plant cells have the plasticity required to produce influenza VLPs derived from their plasma membrane and accumulate them in the apoplastic space.

## Example 6

## Plasma Membrane Lipid Analysis

Further confirmation of the composition and origin of the plant influenza VLPs was obtained from analyses of the lipid content. Lipids were extracted from purified VLPs and their composition was compared to that of highly purified tobacco plasma membranes by high performance thin layer chromatography (HP-TLC). The migration patterns of polar and neutral lipids from VLPs and control plasma membranes were similar. Purified VLPs contained the major phospholipids (phosphatidylcholine and phosphatidylethanolamine) and sphingolipids (glucosyl-ceramide) found in the plasma

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membrane (FIG. 27A), and both contained free sterols as the sole neutral lipids (FIG. 27B). However, immunodetection of a plasma membrane protein marker (ATPase) in purified VLP extracts showed that the VLP lipid bilayer does not contain one of the major proteins associated with plant plasma membranes, suggesting that host proteins may have been excluded from the membranes during the process of VLPs budding from the plant cells (FIG. 27C).

## Example 7

## Immunogenicity of the H5 VLPs and Effect of Route of Administration

Mice were administered plant-made H5 VLPs by intramuscular injection, or intranasal (inhalation). 0.1 to 12  $\mu\text{g}$  of VLPs were injected intramuscularly into mice, with alum as an adjuvant, according to the described methods. Peak antibody titers were observed with the lowest antigen quantity, in a similar magnitude to that of 5  $\mu\text{g}$  recombinant, soluble hemagglutinin (HA) (FIG. 20A).

0.1 to 1  $\mu\text{g}$  plant-made H5 VLPs were administered intranasally with a chitosan adjuvant provided for an antibody response greater than that of the recombinant soluble HA with an alum adjuvant (FIG. 20B).

For both administration routes, and over a range of antigen quantities, seroconversion was observed in all of the mice tested. Recombinant H5 soluble antigen conferred low (<1/40) or negligible (1<1/10 for the non-adjuvanted recombinant H5) HI titres.

## Example 8

## Hemagglutination-Inhibition Antibody Titer (HAI) H5 VLP

FIG. 21A, B illustrates the hemagglutination inhibition (HAI) antibody response 14 days following a "boost" with plant-made H5 VLP, or recombinant soluble HA. The lowest dose of antigen (0.1  $\mu\text{g}$ ) when administered intramuscularly produced a superior HAI response to a 10-fold greater administration (5  $\mu\text{g}$ ) of recombinant soluble HA. Increasing doses of H5 VLP provided a modest increase in HAI over the lowest dose.

HAI response following intranasal administration was significantly increased in mice administered plant-made H5 VLPs (1.0 or 0.1  $\mu\text{g}$ ) compared to those administered 1  $\mu\text{g}$  recombinant soluble HA, which was similar to the negative control. All mice immunized by intramuscular injection of H5 VLPs (from 0.1 to 12  $\mu\text{g}$ ) had higher HAI titers than mice immunised with the control HA antigen (FIG. 4a—now 21A). For the same dose of 5  $\mu\text{g}$ , VLPs induced HAI titers 20 times higher than the corresponding dose of the control HA antigen. VLPs also induced significantly higher HAI titers than the control HA antigen when delivered through the intranasal route (FIG. 21b). For a given dose of H5 VLP the levels of HAI titers were lower in mice immunised intranasally than for mice immunised intramuscularly; 1  $\mu\text{g}$  VLP induced a mean HAI titer of 210 when administered i.m. while the same dose induced a mean HAI titer of 34 administered i.n.

When administered intramuscularly, all doses of VLPs induced high level of antibodies capable of binding homologous whole inactivated viruses (FIGS. 20b and 24). No significant difference was found between the plant-made VLP vaccine and the control HA antigen (except the 12  $\mu\text{g}$  VLP group 14 days after boost), as both antigen preparations

induce high binding antibody titers against the homologous strain. However, when administered intranasally, VLPs induced higher binding antibody titers in than did the control HA antigen (FIG. 20b). When mixed with Chitosan, immunization with one microgram VLP induced a reciprocal mean Ab titer of 5 500, 8.6 times higher than the level found in mice immunized with 1 µg of the control HA antigen (reciprocal mean Ab titer of 920).

The immunogenicity of the plant-derived influenza VLPs was then investigated through a dose-ranging study in mice. Groups of five BALB/c mice were immunized intramuscularly twice at 3-week intervals with 0.1 µg to 12 µg of VLPs containing HA from influenza A/Indonesia/5/05 (H5N1) formulated in alum (1:1 ratio). Hemagglutination-inhibition titers (HI), using whole inactivated virus antigen (A/Indonesia/5/05 (H5N1)), were measured on sera collected 14 days after the second immunization. Immunization with doses of VLP as low as 0.1 µg induced the production of antibodies that inhibited viruses from agglutinating erythrocytes at high dilutions (FIG. 21A). Parallel immunization of mice with 5 µg of non-VLP alum-adjuvanted control H5 antigen (also from A/Indonesia/5/05) induce an HI response that was 2-3 logs lower than that achieved with the lowest VLP dose.

For both administration routes, and over a range of antigen quantities, the HAI response is superior in mice administered VLPs.

#### Example 9

##### Effect of Adjuvant on Immunogenicity of H5 VLPs

Plant-made H5 VLPs have a plasma membrane origin (FIG. 19, Example 5). Without wishing to be bound by theory, enveloped viruses or VLPs of enveloped viruses generally acquire their envelope from the membrane they bud through. Plant plasma membranes have a phytosterol complement that is rarely, if ever found in animal cells, and several of these sterols have been demonstrated to exhibit immunostimulatory effects.

Plant-made H5 VLPs were administered intramuscularly (FIG. 22A) or intranasally (FIG. 22B) to mice in the presence or absence of an adjuvant, and the HAI (hemagglutination inhibition antibody response) determined VLPs, in the presence or absence of an added adjuvant (alum or chitosan, as in these examples) in either system of administration demonstrated a significantly greater HAI hemagglutinin inhibition than recombinant soluble HA. Even in the absence of an added adjuvant (i.e. alum or chitosan), plant-made H5 VLPs demonstrate a significant HAI, indicative of a systemic immune response to administration of the antigen.

Alum enhanced the mean level of HAI titers by a factor of 5 for intramuscular administration of VLP (FIG. 22a) and by a factor of 3.7 for the control HA antigen. When administered i.m., 5 µg VLPs induced a mean HAI titer 12 times higher than the corresponding dose of control HA antigen. Chitosan did not boost the mean HAI level of the control HA antigen (FIG. 22b) while it increased the mean HAI level of mice immunised with 1 µg VLP administered i.n. by a factor of 5-fold.

#### Example 10

##### Antibody Isotypes

Mice administered plant-made H5 VLPs or recombinant soluble HA in the presence or absence of alum as an added adjuvant demonstrate a variety of immunoglobulin isotypes (FIG. 23A).

In the presence of an added adjuvant, the antibody isotype profiles of VLPs and the HA are similar, with IgG1 being the dominant isotype. When VLPs or HA are administered without an added adjuvant, IgG1 response is reduced, but remains the dominant isotype response to VLPs, with IgM, IgG2a, IgG2B and IgG3 maintaining similar titers as in the presence of an added adjuvant. IgG1, IgG2a, and IgG2b titers are markedly reduced when HA is administered without an added adjuvant.

These data, therefore, demonstrate that plant-made VLPs do not require an added adjuvant to elicit a antibody response in a host.

Antibody titers against whole inactivated influenza virus strains (A/Indonesia/5/05; A/Vietnam/1203/04)I in mice administered plant-made VLPs or soluble recombinant HA intramuscularly in the presence of an added antigen are illustrated in FIG. 23B. No significant difference is observed in the antibody titers for these influenza strains in mice administered 1 ug or 5 ug of VLPs or 5 ug of soluble HA.

#### Example 11

##### Cross-Reactivity of Serum Antibodies Induced by the H5 VLP Vaccine

Cross-reactivity of serum antibodies induced by H5 VLP was assessed against whole inactivated influenza viruses of different strains. All VLP doses (from 0.1 to 12 µg) as well as 5 µg of control HA antigen induced high binding antibody titers against a clade 1 strain (A/Vietnam/1194/04), the homologous strain A/Indonesia/5/05 of clade 2.1, and a clade 2.2 strain A/turkey/Turkey/1/05 (FIG. 25A).

However, only the plant-made VLP induced HAI titer against the A/turkey/Turkey/1/05 strain (FIG. 25b). HAI titers for the A/Indonesia/5/05 were high for VLPs.

#### Example 12

##### Cross-Protection Conferred by Immunization with Plant-Made H5 VLP

Mice that previously had been administered a two-dose regimen of A/Indonesia/5/05 H5 VLPs as described, were subsequently challenged intranasally with influenza A/Turkey/582/06 (H5N1) ("Turkey H5N1") infectious virus, and observed. The dose administered, per animal, was 10 LD<sub>50</sub> (4.09×10<sup>5</sup> CCID<sub>50</sub>).

By 7 days post-challenge, only 37.5% of the mice administered the PBS vaccine control had survived exposure to Turkey H5N1 (FIG. 26A). 100% of animals administered the control antigen (HA) or 1, 5 or 15 ug of Indonesia H5 VLPs survived up to 17 days post-challenge, when the experiment was terminated.

Body mass of the mice was also monitored during the experiment, and the average mass of the surviving mice plotted (FIG. 26B). Mice administered 1, 5 or 15 ug of the Indonesia H5 VLPs before challenge did not lose any appreciable mass during the course of the experiment, and in particular mice administered 5 ug of the VLPs appear to have gained significant mass. Negative control mice (no Turkey H5N1 challenge) did not appreciably gain or lose body mass. Positive control mice (not administered VLPs, but challenged with Turkey H5N1) exhibited significant loss of body mass during the course of the experiment, and three of these mice died. As body mass is an average of all mice in the cohort, removal of the 'sickest' mice (the 3 that died) may lead to an apparent overall increase in mass, however

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note that the average body mass of the positive control cohort is still significantly below that of the negative or the VLP-treated cohorts.

These data, therefore, demonstrate that plant-made influenza VLPs comprising the H5 hemagglutinin viral protein induce an immune response specific for pathogenic influenza strains, and that virus-like particles may bud from a plant plasma membrane.

These data, therefore, demonstrate that plants are capable of producing influenza virus-like particles, and also for the first time, that virus-like particles can bud from a plant plasma membrane.

Further, using the current transient expression technology, a first antigen lot was produced only 16 days after the sequence of the target HA was obtained. Under the current yields for H5 VLPs, and at an exemplary dose of 5 µg per subject, each kg of infiltrated leaf may produce ~20,000 vaccine doses. This unique combination of platform simplicity, surge capacity and powerful immunogenicity provides for, among other embodiments, a new method response in the context of a pandemic.

#### Example 13

##### Characterization of Hemagglutinin-Containing Structures in Plant Extracts Using Size Exclusion Chromatography

The assembly of plant-produced influenza hemagglutinin of different subtypes into high molecular weight structures was assessed by gel filtration. Crude or concentrated protein extracts from AGL1/660-, AGL1/540-, AGL1/783-, AGL1/780- and AGL1/785-infiltrated plants (1.5 mL) were fractionated by size exclusion chromatography (SEC) on Sephacryl™ S-500 HR columns (GE Healthcare Bio-Science Corp., Piscataway, N.J., USA). As shown in FIG. 46, Blue Dextran (2 MDa) elution peaked early in fraction 10. When proteins from 200 µL of each SEC elution fraction were concentrated (5-fold) by acetone-precipitation and analyzed by Western blotting (FIG. 46), hemagglutinins were primarily found in fractions 7 to 14, and are indicative of the incorporation of HA into VLPs. Without wishing to be bound by theory, this suggests that the HA protein had either assembled into a large superstructure or that it has attached to a high molecular weight structure, irrespectively of the subtype produced.

#### Example 14

##### Transient Expression of Seasonal Influenza Virus Hemagglutinin by Agroinfiltration in *N. benthamiana* Plants

The ability of the transient expression system to produce seasonal influenza hemagglutinins was determined through the expression of the H1 subtype from strains A/Brisbane/59/2007 (H1N1) (plasmid #774), A/New Caledonia/20/1999 (H1N1) (plasmid #540) and A/Solomon Islands/3/2006 (H1N1) (plasmid #775). The hemagglutinin gene coding sequences were first assembled in the plastocyanin expression cassette—promoter, 5'UTR, 3'UTR and transcription termination sequences from the alfalfa plastocyanin gene—and the assembled cassettes were inserted into to a pCAMBIA binary plasmid. The plasmids were then transfected into *Agrobacterium* (AGL1), producing *Agrobacterium* strains AGL1/774, AGL1/540 and AGL1/775, respectively.

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*N. benthamiana* plants were infiltrated with AGL1/774, AGL1/540 and AGL1/775, and the leaves were harvested after a six-day incubation period. To determine whether H1 accumulated in the agroinfiltrated leaves, protein were first extracted from infiltrated leaf tissue and analyzed by Western blotting using anti-H1 antibodies. A unique band of approximately 72 kDa was detected in extracts (FIG. 47), corresponding in size to the uncleaved HA0 form of influenza hemagglutinin. This demonstrated that expression of different annual epidemic strains of hemagglutinin in infiltrated leaves results in the accumulation of the uncleaved translation product.

#### Example 15

##### Transient Expression of Potential Pandemic Influenza Virus Hemagglutinin by Agroinfiltration in *N. benthamiana* Plants

The ability of the transient expression system to produce potential influenza hemagglutinins was determined through the expression of the H5 subtype from strains A/Anhui/1/2005 (H5N1) (plasmid #781), A/Indonesia/5/2005 (H5N1) (plasmid #660) and A/Vietnam/1194/2004 (H5N1) (plasmid #782). The hemagglutinin gene coding sequences were first assembled in the plastocyanin expression cassette—promoter, 5'UTR, 3'UTR and transcription termination sequences from the alfalfa plastocyanin gene—and the assembled cassettes were inserted into to a pCAMBIA binary plasmid. The plasmids were then transfected into *Agrobacterium* (AGL1).

*N. benthamiana* plants were infiltrated with AGL1/781, AGL1/660 and AGL1/782, and the leaves were harvested after a six-day incubation period. To determine whether H5 accumulated in the agroinfiltrated leaves, protein were first extracted from infiltrated leaf tissue and analyzed by Western blotting using anti-H5 antibodies. A unique band of approximately 72 kDa was detected in extracts (FIG. 48), corresponding in size to the uncleaved HA0 form of influenza hemagglutinin. This demonstrated that expression of different potential pandemic strains of hemagglutinin in infiltrated leaves results in the accumulation of the uncleaved translation product.

#### Example 16

##### Transient Expression of H5 by Agroinfiltration in *N. tabacum* Plants

The ability of the transient expression system to produce influenza hemagglutinin in leaves of *Nicotiana tabacum* was analysed through the expression of the H5 subtype from strain A/Indonesia/5/2005 (H5N1) (plasmid #660). The hemagglutinin gene coding sequences were first assembled in the plastocyanin expression cassette—promoter, 5'UTR, 3'UTR and transcription termination sequences from the alfalfa plastocyanin gene—and the assembled cassettes were inserted into to a pCAMBIA binary plasmid. The plasmids were then transfected into *Agrobacterium* (AGL1).

*N. tabacum* plants were infiltrated with AGL1/660 and the leaves were harvested after a six-day incubation period. To determine whether H5 accumulated in the agroinfiltrated leaves, protein were first extracted from infiltrated leaf tissue and analyzed by Western blotting using anti-H5 antibodies. A unique band of approximately 72 kDa was detected in extracts (FIG. 49), corresponding in size to the uncleaved HA0 form of influenza hemagglutinin. This demonstrated

that expression of hemagglutinin in infiltrated *N. tabacum* leaves results in the accumulation of the uncleaved translation product.

## Example 17

## Immunogenicity of Plant-Made H5N1 VLP Vaccine from A/Indonesia/5/05 (H5N1) in Ferrets

A dose escalation study in ferrets was performed to evaluate the immunogenicity of plant derived VLPs. In vitro cross-reactivity of serum antibody induced by the H5 VLP vaccine at 3 doses (1, 5 and 15 ug) was assessed by hemagglutination inhibition of three other H5N1 strains—A/turkey/Turkey/1/05 (clade 2.2), A/Vietnam/1194/04 (clade 1) and A/Anhui/5/05 (all whole, inactivated virus), using serum taken 14 days after the first dose of vaccine (FIG. 50A), and 14 days after the 2<sup>nd</sup> dose (FIG. 50 B). For all 3 dose concentrations, cross-reactivity is observed

## Example 17

## Analysis of the Immunogenicity Results According to CHMP Criteria

The EMEA's Committee for Medicinal Products for Human Use (CHMP) (<http://www.emea.europa.eu/htms/general/contacts/CHMP/CHMP.html>) sets out three criteria (applied following the second dose) for vaccine efficacy: 1—Number of seroconversion or significant increase in HI titers (4-fold)>40%; 2—Mean geometric increase of at least 2.5; 3—proportion of subjects achieving an HI titer of 1/40 should be at least 70%. Analysis of these criteria in the ferret model is shown in Tables 8-11. (\*) is indicative of meeting or exceeding the CHMP criteria. A summary of cross-immunogenicity analysis in relation to CHMP criteria for licensure is shown in Table 12.

Animals were assessed daily for body weight, temperature and overall condition. No sign of sickness or discomfort was recorded during the study. Body weight and temperature was within normal ranges during the study. The vaccine was safe and tolerated by the study animals.

TABLE 8

Data for homologous strain (A/Indonesia/5/05)										
		Study group								
Day	Criteria	1 µg	1 µg adjuvanted	5 µg	5 µg adjuvanted	7.5 µg	15 µg	15 µg adjuvanted	30 µg	5 µg ITC
14 (post 1st inj.)	% 4-fold increase in HI titer	0%	100%	0%	100%*	20%	20%	80%*	0%	0%
	Mean geometric increase	0%	7.6	0%	15.6*	1.3	1.2	11.2*	0%	0%
	% of HI titer of 1/40	0%	60%	0%	100%*	20%	0%	80%*	0%	0%
	Mean HI titer		38		78			56		
35 (14 days post boost)	% 4-fold increase in HI titer	0%	100%*	0%	60%*	0%	0%	40%*	0%	0%
	Mean geometric increase	0%	10.8*	0%	5.9*	0.7	0%	4*	0%	0%
	% of HI titer of 1/40	0%	100%*	0%	100%*	0%	0%	100%*	0%	0%
	Mean HI titer		411		465			217		

TABLE 9

Data for heterologous strain (A/Vietnam/1194/04)										
		Study group								
Day	Criteria	1 µg	1 µg adjuvanted	5 µg	5 µg adjuvanted	7.5 µg	15 µg	15 µg adjuvanted	30 µg	5 µg ITC
14 (post 1st inj.)	% 4-fold increase in HI titer		0%		0%				0%	
	Mean geometric increase		1.2		1.2			1.3		
	% of HI titer of 1/40		0%		0%			0%		
35 (post boost)	% 4-fold increase in HI titer		60%		80%*			60%		
	Mean geometric increase		2.3		5.1*			1.78		
	% of HI titer of 1/40		0%		80%*			20%		

TABLE 10

Data for heterologous strain (A/turkey/Turkey/1/05)										
		Study group								
Day	Criteria	1 µg	1 µg adjuvanted	5 µg	5 µg adjuvanted	7.5 µg	15 µg	15 µg adjuvanted	30 µg	5 µg ITC
14 (post 1st inj.)	% 4-fold increase in HI titer		40%		20%			60%		
	Mean geometric increase		1.9		1.7			2.8		
	% of HI titer of 1/40		40%		20%			40%		

TABLE 10-continued

Data for heterologous strain (A/turkey/Turkey/1/05)										
Day	Criteria	Study group								
		1 µg	1 µg adjuvanted	5 µg	5 µg adjuvanted	7.5 µg	15 µg	15 µg adjuvanted	30 µg	5 µg ITC
35 (post boost)	% 4-fold increase in HI titer		80%*		100%*				80%*	
	Mean geometric increase		10.6*		20.8*				7.7*	
	% of HI titer of 1/40		100%*		100%*				100%*	

TABLE 11

Data for heterologous strain (A/Anhui/5/05)										
Day	Criteria	Study group								
		1 µg	1 µg adjuvanted	5 µg	5 µg adjuvanted	7.5 µg	15 µg	15 µg adjuvanted	30 µg	5 µg ITC
14 (post 1st inj.)	% 4-fold increase in HI titer		40%		20%				80%*	
	Mean geometric increase		1.8		1.3				6.4*	
	% of HI titer of 1/40		20%		20%				80%*	
35 (post boost)	% 4-fold increase in HI titer		100%*		100%*				60%*	
	Mean geometric increase		11.8*		14.4*				3*	
	% of HI titer of 1/40		100%*		80%*				80%*	

TABLE 12

Summary of cross-immunogenicity analysis in relation to CHMP criteria for licensure.				
Strain	Criteria	Study group		
		1 µg adjuvanted	5 µg adjuvanted	15 µg adjuvanted
A/turkey/Turkey/1/05	% 4-fold increase in HI titer	80%*	100%*	80%*
(clade 2.2)	Mean geometric increase	10.6*	20.8*	7.7*
	% of HI titer of 1/40	100%*	100%*	100%*
A/Anhui/1/05	% 4-fold increase in HI titer	100%*	100%*	60%*
(clade 2.3)	Mean geometric increase	11.8*	14.4*	3*
	% of HI titer of 1/40	100%*	80%*	80%*
A/Vietnam/1194/04	% 4-fold increase in HI titer	60%	80%*	60%
(clade 1)	Mean geometric increase	2.3	7.1*	1.78
	% of HI titer of 1/40	0%	80%*	20%

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Example 18

Selection of Heagglutinin Nucleotide Sequences

The nucleotide sequences of the HA were retrieved from an influenza sequence database, or the NCBI influenza virus resource. For several of the HA nucleic acid sequences, multiple entries are listed in the databases (Table 13). Some variation is associated primarily with the culture system (Origin—MDCK, egg, unknown, viral RNA/clinical isolate); for example, the glycosylation site at position 194 (mature protein numbering) of the HA is absent when type B influenza virus is expressed in allantoic fluid of eggs (see also Chen et al., 2008). For some sequences, domains may be lacking (e.g. incomplete clones, sequencing artifacts, etc.). The hemagglutinin sequence may be divided into 5 domains: signal peptide (SP), HA1, HA2, transmembrane (DTm) and cytoplasmic tail. Domains of a first sequence may be combined with a domain from a second existing sequence e.g. the signal peptide of a first strain sequence may be combined with the balance of the hemagglutinin coding sequence from a second strain to provide a complete coding sequence.

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TABLE 13

Variation in Influenza subtypes for selected HA coding sequences									
Strain	Sequence database reference	Origin	SP	HA1	HA2	DTm	Divergence	No.	
H1 A/Solomon Islands/3/2006	ISDN231558 (Vaccine rec.)	MDCK	Y	Y	Y	Y	189: R ou G, 220: K (MDCK) T(Egg), 249: Q (MDCK) R(Egg), 550: L (MDCK) R (Egg)		
	ISDN238190	Egg	Y	Y	Y	Y	189: R ou G, 220: K (MDCK) T(Egg), 249: Q (MDCK) R(Egg), 550: L (MDCK) R (Egg)		

TABLE 13-continued

Variation in Influenza subtypes for selected HA coding sequences							
Strain	Sequence database reference No.	Origin	SP	HA1	HA2	DTm	Divergence
A/Solomon Islands/3/2006	EU100724	?	Y	Y	Y	Y	189: R ou G, 220: K (MDCK) T(Egg), 249: Q (MDCK) R(Egg), 550: L (MDCK) R (Egg)
A/Solomon Islands/3/2006	ISDN220951	MDCK	Y	Y	N	N	189: R ou G, 220: K (MDCK) T(Egg), 249: Q (MDCK) R(Egg), 550: L (MDCK) R (Egg)
A/Solomon Islands/3/2006	ISDN220953	Egg	Y	Y	N	N	189: R ou G, 220: K (MDCK) T(Egg), 249: Q (MDCK) R(Egg), 550: L (MDCK) R (Egg)
A/Solomon Islands/3/2006	EU124137	Egg	Y	Y	N	N	189: R ou G, 220: K (MDCK) T(Egg), 249: Q (MDCK) R(Egg), 550: L (MDCK) R (Egg)
A/Solomon Islands/3/2006	EU124135	MDCK	Y	Y	N	N	189: R ou G, 220: K (MDCK) T(Egg), 249: Q (MDCK) R(Egg), 550: L (MDCK) R (Egg)
A/Solomon Islands/3/2006	EU124177	MDCK	Y	Y	Y	Y	189: R ou G, 220: K (MDCK) T(Egg), 249: Q (MDCK) R(Egg), 550: L (MDCK) R (Egg)
H1 A/Brisbane/59/2007	ISDN282676	MDCK	Y	Y	Y		203: D/I/N D est le plus abondant chez les H1
A/Brisbane/59/2007	ISDN285101	Egg	Y	Y	N	N	203: D/I/N D est le plus abondant chez les H1
A/Brisbane/59/2007	ISDN285777	Egg	Y	Y	Y	Y	203: D/I/N D est le plus abondant chez les H1
A/Brisbane/59/2007	ISDN282677	Egg	Y	Y	Y	Y	203: D/I/N D est le plus abondant chez les H1
H3 A/Brisbane/10/2007	ISDN274893	Egg	Y	Y	Y	Y	202: V/G, 210: L/P, 215: del Ala, 242: S/I
A/Brisbane/10/2007	ISDN257648	MDCK	N	Y	Y	Y	202: V/G, 210: L/P, 215: del Ala, 242: S/I
A/Brisbane/10/2007	ISDN256751	Egg	Y	Y	Y	Y	202: V/G, 210: L/P, 215: del Ala, 242: S/I
A/Brisbane/10/2007	ISDN273757	Egg	Y	Y	Y	Y	202: V/G, 210: L/P, 215: del Ala, 242: S/I
A/Brisbane/10/2007	ISDN273759	Egg	Y	Y	Y	Y	202: V/G, 210: L/P, 215: del Ala, 242: S/I
A/Brisbane/10/2007	EU199248	Egg	N	Y	Y	Y	202: V/G, 210: L/P, 215: del Ala, 242: S/I
A/Brisbane/10/2007	EU199366	Egg	Y	Y	Y	Y	202: V/G, 210: L/P, 215: del Ala, 242: S/I
A/Brisbane/10/2007	ISDN257043	Egg	N	Y	Y	Y	202: V/G, 210: L/P, 215: del Ala, 242: S/I
A/Brisbane/10/2007	EU199250	MDCK	N	Y	Y	Y	202: V/G, 210: L/P, 215: del Ala, 242: S/I
A/Brisbane/10/2007	ISDN275357	Egg	N	Y	N	N	202: V/G, 210: L/P, 215: del Ala, 242: S/I
A/Brisbane/10/2007	ISDN260430	Egg	N	Y	Y	Y	202: V/G, 210: L/P, 215: del Ala, 242: S/I
H3 A/Wisconsin/67/2005	ISDN131464	?	N	Y	Y	N	138: A/S 156: H/Q 186: G/V 196: H/Y
A/Wisconsin/67/2005	DQ865947	?	N	Y	partiel	N	138: A/S 156: H/Q 186: G/V 196: H/Y
A/Wisconsin/67/2005	EF473424	?	N	Y	Y	N	138: A/S 156: H/Q 186: G/V 196: H/Y
A/Wisconsin/67/2005	ISDN138723	Egg	N	Y	Y	Y	138: A/S 156: H/Q 186: G/V 196: H/Y

TABLE 13-continued

Variation in Influenza subtypes for selected HA coding sequences							
Strain	Sequence database reference No.	Origin	SP	HA1	HA2	DTm	Divergence
A/Wisconsin/67/2005	EF473455	Egg	N	Y	Y	Y	138: A/S 156: H/Q 186: G/V 196: H/Y
A/Wisconsin/67/2005	ISDN138724	?	N	Y	Y	Y	138: A/S 156: H/Q 186: G/V 196: H/Y
B B/Malaysia/2506/2004	ISDN126672 (vaccine rec.)	Egg	Y	Y	N	N	120 K/N 210 T/A
B/Malaysia/2506/2004	EF566433	Egg	Y	Y	N	N	120 K/N 210 T/A
B/Malaysia/2506/2004	ISDN231265	Egg	Y	Y	Y	Y	120 K/N 210 T/A
B/Malaysia/2506/2004	ISDN231557	MDCK	Y	Y	Y	Y	120 K/N 210 T/A
B/Malaysia/2506/2004	EF566394	MDCK	Y	Y	N	N	120 K/N 210 T/A
B/Malaysia/2506/2004	EU124274	Egg	Y	Y	Y	Y	120 K/N 210 T/A
B/Malaysia/2506/2004	EU124275	MDCK	Y	Y	Y	Y	120 K/N 210 T/A
B/Malaysia/2506/2004	ISDN124776	MDCK	Y	Y	N	N	120 K/N 210 T/A
B B/Florida/4/2006	ISDN261649	Egg	Y	Y	Y	N	lacking glycosylation site at position 211; 10 amino acids of DTm/cytoplasmic tail
B/Florida/4/2006	EU100604	MDCK	N	Y	N	N	
B/Florida/4/2006	ISDN218061	MDCK	N	Y	N	N	
B/Florida/4/2006	ISDN285778	Egg	Y	Y	Y	Y	Includes cytoplasmic tail
B B/Brisbane/3/2007	ISDN256628	Egg	N	Y	N	N	lacking glycosylation site at position 211
B/Brisbane/3/2007	ISDN263782	Egg	Y	Y	Y	Y	lacking glycosylation site at position 211
B/Brisbane/3/2007	ISDN263783	MDCK	Y	Y	Y	Y	
H5 A/Viet Nam/1194/2004	ISDN38686 (Vaccine rec.)	?	Y	Y	Y	Y	
A/Viet Nam/1194/2004	AY651333	?	Y	Y	Y	Y	
A/Viet Nam/1194/2004	EF541402	?	Y	Y	Y	Y	
H5 A/Anhui/1/2005	DQ37928 (vaccine rec.)	?	Y	Y	Y	Y	
A/Anhui/1/2005	ISDN131465	Egg	Y	Y	Y	Y	
H7 A/Chicken/Italy/13474/1999	AJ91720	ARN gen	Y	Y	Y	Y	
H7 A/Equine/Prague/56	AB298277 (Lab reassortant)	?	Y	Y	Y	Y	152 (R/G) 169 (T/I) 208 (N/D) (glycosylation site abolished)
A/Equine/Prague/56	X62552	?	Y	Y	Y	Y	
H9 A/Hong Kong/1073/1999	AJ404626	?	Y	Y	Y	Y	
A/Hong Kong/1073/1999	AB080226	?	N	Y	N	N	
H2 A/Singapore/1/1957	AB296074	?	Y	Y	Y	Y	
A/Singapore/1/1957	L20410	RNA	Y	Y	Y	Y	

TABLE 13-continued

Variation in Influenza subtypes for selected HA coding sequences							
Strain	Sequence database reference No.	Origin	SP	HA1	HA2	DTm	Divergence
A/Singapore/1/1957	L11142	?	Y	Y	Y	Y	
H2 A/Japan/305/1957	L20406	?	Y	Y	Y	Y	
A/Japan/305/1957	L20407	?	Y	Y	Y	Y	
A/Japan/305/1957	CY014976	?	Y	Y	Y	Y	
A/Japan/305/1957	AY209953	?	Y	Y	N	N	
A/Japan/305/1957	J02127	?	Y	Y	Y	Y	
A/Japan/305/1957	DQ508841	?	Y	Y	Y	Y	
A/Japan/305/1957	AY643086	?	Y	Y	Y	N	
A/Japan/305/1957	AB289337	?	Y	Y	Y	Y	
A/Japan/305/1957	AY643085	?	Y	Y	Y	Y	
A/Japan/305/1957	AY643087	Drug resistant	Y	Y	Y	N	
H6 A/Teal/Hong Kong/W312/1997 (H6N1)	AF250479	Egg	Y	Y	Y	Y	

Y, N—Yes, No, respectively  
 SP—presence of signal peptide sequence Y/N  
 HA1—complete HA1 domain Y/N  
 HA2—complete HA2 domain Y/N  
 DTm—complete transmembrane domain Y/N

Strain: H1 from A/Solomon Islands/3/2006

Eight amino acid sequences were compared, and variations identified. (Table 14). Position 171 exhibited a variation of glycine (G) or arginine (R) in some sequences.

TABLE 14

A/Solomon Islands/3/2006 amino acid variation		
Amino acid #*	MDCK	Egg
212	K	T
241	Q	R
542	L	R

Numbering from the starting M

Strain: H1 from A/Brisbane/59/2007

Position 203 exhibited a variation of aspartic acid (D), isoleucine (I) or asparagine (N).

Strain: H3 from A/Brisbane/10/2007

Sequence variations were observed at 5 positions (Table 15). In position 215, a deletion is observed in two sampled sequences.

TABLE 15

H3 from A/Brisbane/10/2007 amino acid variation						
Origin	202	210	215	235	242*	
ISDN274893	Egg	V	L	—	Y	I
ISDN273759	Egg	G	P	A	S	I
EU199248	Egg	G	P	A	S	I
EU199366	Egg	G	P	A	S	I
ISDN273757	Egg	V	L	—	S	S

35

TABLE 15-continued

H3 from A/Brisbane/10/2007 amino acid variation

40

Origin	202	210	215	235	242*	
ISDN257043	Egg	G	P	A	S	I
EU199250	MDCK	G	L	A	S	I
ISDN375357	Egg	G	P	A	S	I
ISDN260430	Egg	G	P	A	S	I
ISDN256751	Egg	G	P	A	S	I
ISDN257648	MDCK	G	L	A	S	I

\*Numbering from the starting M

50

Strain: H3 from A/Wisconsin/67/2005

Sequence variations in this strain were observed at 4 positions (Table 16).

TABLE 16

H3 from A/Wisconsin/67/2005 amino acid variation						
Origin	138	156	186	196		
ISDN138724	Unknown	A	H	G	H	
DQ865947	Unknown	S	H	V	Y	
EF473424	Unknown	A	H	G	H	
ISDN138723	Egg	S	Q	V	Y	
ISDN131464	Unknown	A	H	G	H	
EF473455	Egg	A	H	G	H	

\*Numbering from the mature protein

Strain: B from B/Malaysia/2506/2004

Variation at two positions is observed (Table 17). Position 120 is not a glycosylation site; position 210 is involved in glycosylation; this glycosylation is abolished following culture in eggs.

TABLE 17

Hemagglutinin from B/Malaysia/2506/2004 amino acid variation		
Amino acid #*	MDCK	Egg
120	K	N
210	T	A

\*Numbering from the middle of SP

Strain: Hemagglutinin from B/Florida/4/2006; ISDN261649

Observed variations include amino acid sequence variation at position 211, depending on the culture system. Asparatine (N) is found in sequences isolated from MDCK cells, while glutamic acid (D) is found in sequence isolated from eggs. Position 211 is a glycosylation site, and is abolished following culture in eggs.

Strain: H2 from A/Singapore/1/1957

Sequence variations were observed in 6 positions (Table 18).

TABLE 18

H2 from A/Singapore/1/1957 amino acid variation							
	Origin	Amino acid No.					
		166	168	199	236	238	358
L20410	Viral RNA	K	E	T	L	S	V
L11142	Unknown	E	G	K	L	S	I
AB296074	Unknown	K	G	T	Q	G	V
Consensus		K	G	T	Q/L	G	V
A/Japan/305/1957							

<sup>1</sup>Numbering from the mature protein

Strains: H5 from A/Vietnam/1194/2004 and H5 from A/Anhui/1/2005

There were no variations observed in the amino acid sequence upon aligning the primary sequences of either of these H5 strains.

Strain: H6 from A/Teal/Hong Kong/W312/1997

Only one entry was available for strain (AF250179).

Strain: H7 from A/Equine/Prague/56

A total of 2 sequence entries were found in the databases. The entry AB298877 was excluded as it is a laboratory reassortant.

Strain: H9 from A/Hong Kong/1073/1999; AJ404626

A total of 2 sequence entries were found in the databases. Only one was complete.

All citations are hereby incorporated by reference.

The present invention has been described with regard to one or more embodiments. However, it will be apparent to persons skilled in the art that a number of variations and modifications can be made without departing from the scope of the invention as defined in the claims.

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<210> SEQ ID NO 8
<211> LENGTH: 1471
<212> TYPE: DNA

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&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Expression Cassette

&lt;400&gt; SEQUENCE: 8

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agaggtaccc cgggctggta ttttatatg ttgtcaaata actcaaaaac cataaaagtt    60
taagttagca agtgtgtaca ttttacttg aacaaaaata ttcacctact actgttataa    120
atcattatta aacattagag taaagaaata tggatgataa gaacaagagt agtgatattt    180
tgacaacaat tttgttgcaa catttgagaa aattttgttg ttctctcttt tcattgggtca    240
aaaacaatag agagagaaaa aggaagaggg agaataaaaa cataatgtga gtatgagaga    300
gaaagttgta caaaagttgt accaaaatag ttgtacaaat atcattgagg aatttgacaa    360
aagctacaca aataagggtt aattgctgta aataaataag gatgacgcat tagagagatg    420
taccattaga gaatttttgg caagtcatta aaaagaaaga ataaattatt tttaaaatta    480
aaagttgagt catttgatta aacatgtgat ttttaatga attgatgaaa gagttggatt    540
aaagttgat  tagtaattag aatttgggtg caaatttaat ttgacatttg atcttttctt    600
atatattgcc ccatagagtc agttaactca tttttatatt tcatagatca aataagagaa    660
ataacggtat attaatccct ccaaaaaaaaa aaaacggtat atttactaaa aaatctaagc    720
cacgtaggag gataacagga tccccgtagg aggataacat ccaatccaac caatcacaac    780
aatcctgatg agataacca cttaaagccc acgcatctgt ggcacatcta cattatctaa    840
atcacacatt cttccacaca tctgagccac acaaaaacca atccacatct ttatcaccca    900
ttctataaaa aatcacactt tgtgagtcta cactttgatt cccttcaaac acatacaaag    960
agaagagact aattaattaa ttaatcatct tgagagaaaa tggcgaaaaa cgttgcgatt   1020
ttcggcttat tgttttctct tcttgtgttg gttccttctc agatctgagc tctaagttaa   1080
aatgcttctt cgtctcctat ttataatag gtttgttatt gttaattttg ttctttaga    1140
agagcttaat taatcgttgt tgttatgaaa tactatttgt atgagatgaa ctgggtgtaat   1200
gtaattcatt tacataagtg gagtcagaat cagaatgttt cctccataac taactagaca   1260
tgaagacctg ccgctgacaa ttgtcttata ttgaaacaac taaaattgaa catcttttgc   1320
cacaacttta taagtgggta atatagctca aatatatggt caagttcaat agattaataa   1380
tggaatatc agttatcgaa attcattaac aatcaactta acgttattaa ctactaattt   1440
tatatcatcc cctttgataa atgatagtac a                                     1471

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&lt;210&gt; SEQ ID NO 9

&lt;211&gt; LENGTH: 565

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Influenza Virus

&lt;400&gt; SEQUENCE: 9

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Met Lys Ala Lys Leu Leu Val Leu Leu Cys Thr Phe Thr Ala Thr Tyr
 1             5             10             15
Ala Asp Thr Ile Cys Ile Gly Tyr His Ala Asn Asn Ser Thr Asp Thr
 20             25             30
Val Asp Thr Val Leu Glu Lys Asn Val Thr Val Thr His Ser Val Asn
 35             40             45
Leu Leu Glu Asp Ser His Asn Gly Lys Leu Cys Leu Leu Lys Gly Ile
 50             55             60
Ala Pro Leu Gln Leu Gly Asn Cys Ser Val Ala Gly Trp Ile Leu Gly
 65             70             75             80

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Asn	Pro	Glu	Cys	Glu	Leu	Leu	Ile	Ser	Lys	Glu	Ser	Trp	Ser	Tyr	Ile	85	90	95	
Val	Glu	Thr	Pro	Asn	Pro	Glu	Asn	Gly	Thr	Cys	Tyr	Pro	Gly	Tyr	Phe	100	105	110	
Ala	Asp	Tyr	Glu	Glu	Leu	Arg	Glu	Gln	Leu	Ser	Ser	Val	Ser	Ser	Phe	115	120	125	
Glu	Arg	Phe	Glu	Ile	Phe	Pro	Lys	Glu	Ser	Ser	Trp	Pro	Asn	His	Thr	130	135	140	
Val	Thr	Gly	Val	Ser	Ala	Ser	Cys	Ser	His	Asn	Gly	Lys	Ser	Ser	Phe	145	150	155	160
Tyr	Arg	Asn	Leu	Leu	Trp	Leu	Thr	Gly	Lys	Asn	Gly	Leu	Tyr	Pro	Asn	165	170	175	
Leu	Ser	Lys	Ser	Tyr	Val	Asn	Asn	Lys	Glu	Lys	Glu	Val	Leu	Val	Leu	180	185	190	
Trp	Gly	Val	His	His	Pro	Pro	Asn	Ile	Gly	Asn	Gln	Arg	Ala	Leu	Tyr	195	200	205	
His	Thr	Glu	Asn	Ala	Tyr	Val	Ser	Val	Val	Ser	Ser	His	Tyr	Ser	Arg	210	215	220	
Arg	Phe	Thr	Pro	Glu	Ile	Ala	Lys	Arg	Pro	Lys	Val	Arg	Asp	Gln	Glu	225	230	235	240
Gly	Arg	Ile	Asn	Tyr	Tyr	Trp	Thr	Leu	Leu	Glu	Pro	Gly	Asp	Thr	Ile	245	250	255	
Ile	Phe	Glu	Ala	Asn	Gly	Asn	Leu	Ile	Ala	Pro	Trp	Tyr	Ala	Phe	Ala	260	265	270	
Leu	Ser	Arg	Gly	Phe	Gly	Ser	Gly	Ile	Ile	Thr	Ser	Asn	Ala	Pro	Met	275	280	285	
Asp	Glu	Cys	Asp	Ala	Lys	Cys	Gln	Thr	Pro	Gln	Gly	Ala	Ile	Asn	Ser	290	295	300	
Ser	Leu	Pro	Phe	Gln	Asn	Val	His	Pro	Val	Thr	Ile	Gly	Glu	Cys	Pro	305	310	315	320
Lys	Tyr	Val	Arg	Ser	Ala	Lys	Leu	Arg	Met	Val	Thr	Gly	Leu	Arg	Asn	325	330	335	
Ile	Pro	Ser	Ile	Gln	Ser	Arg	Gly	Leu	Phe	Gly	Ala	Ile	Ala	Gly	Phe	340	345	350	
Ile	Glu	Gly	Gly	Trp	Thr	Gly	Met	Val	Asp	Gly	Trp	Tyr	Gly	Tyr	His	355	360	365	
His	Gln	Asn	Glu	Gln	Gly	Ser	Gly	Tyr	Ala	Ala	Asp	Gln	Lys	Ser	Thr	370	375	380	
Gln	Asn	Ala	Ile	Asn	Gly	Ile	Thr	Asn	Lys	Val	Asn	Ser	Val	Ile	Glu	385	390	395	400
Lys	Met	Asn	Thr	Gln	Phe	Thr	Ala	Val	Gly	Lys	Glu	Phe	Asn	Lys	Leu	405	410	415	
Glu	Arg	Arg	Met	Glu	Asn	Leu	Asn	Lys	Lys	Val	Asp	Asp	Gly	Phe	Leu	420	425	430	
Asp	Ile	Trp	Thr	Tyr	Asn	Ala	Glu	Leu	Leu	Val	Leu	Leu	Glu	Asn	Glu	435	440	445	
Arg	Thr	Leu	Asp	Phe	His	Asp	Ser	Asn	Val	Lys	Asn	Leu	Tyr	Glu	Lys	450	455	460	
Val	Lys	Ser	Gln	Leu	Lys	Asn	Asn	Ala	Lys	Glu	Ile	Gly	Asn	Gly	Cys	465	470	475	480
Phe	Glu	Phe	Tyr	His	Lys	Cys	Asn	Asn	Glu	Cys	Met	Glu	Ser	Val	Lys	485	490	495	
Asn	Gly	Thr	Tyr	Asp	Tyr	Pro	Lys	Tyr	Ser	Glu	Glu	Ser	Lys	Leu	Asn				

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500					505					510					
Arg	Glu	Lys	Ile	Asp	Gly	Val	Lys	Leu	Glu	Ser	Met	Gly	Val	Tyr	Gln
		515						520					525		
Ile	Leu	Ala	Ile	Tyr	Ser	Thr	Val	Ala	Ser	Ser	Leu	Val	Leu	Leu	Val
	530					535					540				
Ser	Leu	Gly	Ala	Ile	Ser	Phe	Trp	Met	Cys	Ser	Asn	Gly	Ser	Leu	Gln
545					550					555					560
Cys	Arg	Ile	Cys	Ile											
				565											
<210> SEQ ID NO 10															
<211> LENGTH: 568															
<212> TYPE: PRT															
<213> ORGANISM: Influenza Virus															
<400> SEQUENCE: 10															
Met	Glu	Lys	Ile	Val	Leu	Leu	Leu	Ala	Ile	Val	Ser	Leu	Val	Lys	Ser
1				5					10					15	
Asp	Gln	Ile	Cys	Ile	Gly	Tyr	His	Ala	Asn	Asn	Ser	Thr	Glu	Gln	Val
		20						25					30		
Asp	Thr	Ile	Met	Glu	Lys	Asn	Val	Thr	Val	Thr	His	Ala	Gln	Asp	Ile
		35					40					45			
Leu	Glu	Lys	Thr	His	Asn	Gly	Lys	Leu	Cys	Asp	Leu	Asp	Gly	Val	Lys
	50					55					60				
Pro	Leu	Ile	Leu	Arg	Asp	Cys	Ser	Val	Ala	Gly	Trp	Leu	Leu	Gly	Asn
65					70					75					80
Pro	Met	Cys	Asp	Glu	Phe	Ile	Asn	Val	Pro	Glu	Trp	Ser	Tyr	Ile	Val
			85						90					95	
Glu	Lys	Ala	Asn	Pro	Thr	Asn	Asp	Leu	Cys	Tyr	Pro	Gly	Ser	Phe	Asn
			100					105					110		
Asp	Tyr	Glu	Glu	Leu	Lys	His	Leu	Leu	Ser	Arg	Ile	Asn	His	Phe	Glu
		115					120					125			
Lys	Ile	Gln	Ile	Ile	Pro	Lys	Ser	Ser	Trp	Ser	Asp	His	Glu	Ala	Ser
	130					135					140				
Ser	Gly	Val	Ser	Ser	Ala	Cys	Pro	Tyr	Leu	Gly	Ser	Pro	Ser	Phe	Phe
145					150					155					160
Arg	Asn	Val	Val	Trp	Leu	Ile	Lys	Lys	Asn	Ser	Thr	Tyr	Pro	Thr	Ile
			165						170					175	
Lys	Lys	Ser	Tyr	Asn	Asn	Thr	Asn	Gln	Glu	Asp	Leu	Leu	Val	Leu	Trp
			180					185					190		
Gly	Ile	His	His	Pro	Asn	Asp	Ala	Ala	Glu	Gln	Thr	Arg	Leu	Tyr	Gln
		195					200					205			
Asn	Pro	Thr	Thr	Tyr	Ile	Ser	Ile	Gly	Thr	Ser	Thr	Leu	Asn	Gln	Arg
	210					215					220				
Leu	Val	Pro	Lys	Ile	Ala	Thr	Arg	Ser	Lys	Val	Asn	Gly	Gln	Ser	Gly
225					230					235					240
Arg	Met	Glu	Phe	Phe	Trp	Thr	Ile	Leu	Lys	Pro	Asn	Asp	Ala	Ile	Asn
			245						250					255	
Phe	Glu	Ser	Asn	Gly	Asn	Phe	Ile	Ala	Pro	Glu	Tyr	Ala	Tyr	Lys	Ile
			260					265					270		
Val	Lys	Lys	Gly	Asp	Ser	Ala	Ile	Met	Lys	Ser	Glu	Leu	Glu	Tyr	Gly
		275					280					285			
Asn	Cys	Asn	Thr	Lys	Cys	Gln	Thr	Pro	Met	Gly	Ala	Ile	Asn	Ser	Ser
	290					295					300				

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Met Pro Phe His Asn Ile His Pro Leu Thr Ile Gly Glu Cys Pro Lys  
 305 310 315 320

Tyr Val Lys Ser Asn Arg Leu Val Leu Ala Thr Gly Leu Arg Asn Ser  
 325 330 335

Pro Gln Arg Glu Ser Arg Arg Lys Lys Arg Gly Leu Phe Gly Ala Ile  
 340 345 350

Ala Gly Phe Ile Glu Gly Gly Trp Gln Gly Met Val Asp Gly Trp Tyr  
 355 360 365

Gly Tyr His His Ser Asn Glu Gln Gly Ser Gly Tyr Ala Ala Asp Lys  
 370 375 380

Glu Ser Thr Gln Lys Ala Ile Asp Gly Val Thr Asn Lys Val Asn Ser  
 385 390 395 400

Ile Ile Asp Lys Met Asn Thr Gln Phe Glu Ala Val Gly Arg Glu Phe  
 405 410 415

Asn Asn Leu Glu Arg Arg Ile Glu Asn Leu Asn Lys Lys Met Glu Asp  
 420 425 430

Gly Phe Leu Asp Val Trp Thr Tyr Asn Ala Glu Leu Leu Val Leu Met  
 435 440 445

Glu Asn Glu Arg Thr Leu Asp Phe His Asp Ser Asn Val Lys Asn Leu  
 450 455 460

Tyr Asp Lys Val Arg Leu Gln Leu Arg Asp Asn Ala Lys Glu Leu Gly  
 465 470 475 480

Asn Gly Cys Phe Glu Phe Tyr His Lys Cys Asp Asn Glu Cys Met Glu  
 485 490 495

Ser Ile Arg Asn Gly Thr Tyr Asn Tyr Pro Gln Tyr Ser Glu Glu Ala  
 500 505 510

Arg Leu Lys Arg Glu Glu Ile Ser Gly Val Lys Leu Glu Ser Ile Gly  
 515 520 525

Thr Tyr Gln Ile Leu Ser Ile Tyr Ser Thr Val Ala Ser Ser Leu Ala  
 530 535 540

Leu Ala Ile Met Met Ala Gly Leu Ser Leu Trp Met Cys Ser Asn Gly  
 545 550 555 560

Ser Leu Gln Cys Arg Ile Cys Ile  
 565

<210> SEQ ID NO 11  
 <211> LENGTH: 1629  
 <212> TYPE: DNA  
 <213> ORGANISM: Influenza A Virus

<400> SEQUENCE: 11

gacaaaatat gtcttgggca ccatgctgtg gcaaatggaa caaaagtgaa cacattaaca	60
gagaggggga ttgaagtagt gaacgccaca gagacggtgg aaactgcgaa tatcaagaaa	120
atatgtattc aagggaaaag gccaacagat ctgggacaat gtggacttct aggaacccta	180
ataggacctc cccaatgtga tcaattoctg gagttttact ctgatttgat aattgagcga	240
agagaaggaa ccgatgtgtg ctatccgggt aaattcacia atgaagaatc actgaggcag	300
atccttcgag ggtcaggagg aattgataag gagtcaatgg gtttcaccta tagtgggaata	360
agaaccaatg gagcgacaag tgcctgcaaa agatcaggtt cttctttcta tgcagagatg	420
aagtggttgc tgtcgaattc agacaatgcg gcattccctc aaatgacaaa gtcgataga	480
aatcccagaa acaaacaccg tctgataaatt tggggagttc atcactctgg atcggttagc	540
gagcagacca aactctatgg aagtggaaac aagttgataa cagtaggaag ctcaaaatac	600

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cagcaatcat tcacccaag tccgggagca cggccacaag tgaatggaca atcagggaga	660
atcgattttc actggctact ccttgatccc aatgacacag tgaccttcac tttcaatggg	720
gcattcatag ccctgacag ggcaagtffc tttagaggag aatcactagg agtccagagt	780
gatgttctc tggattctag ttgtggagg gattgcttc acagtggggg tacgatagtc	840
agtccctgc cattccaaa catcaaccct agaactgtgg ggagatgcc tcggtatgtc	900
aaacagacaa gcctcctttt ggctacagga atgagaaatg ttccagagaa tccaaagccc	960
agaggccttt ttggagcaat tgctggattc atagagaatg gatgggaggg tctcatcgat	1020
ggatgggatg gtttcagaca tcaaaatgca caaggggaag gaactgcagc tgactacaaa	1080
agcaccat ctgcaataga tcagatcaca ggcaaatga atcgtctgat tgacaaaaca	1140
aatcagcagt ttgagctgat agacaatgag ttcaatgaga tagaacaaca aataggaaat	1200
gtcattaatt ggacacgaga cgcaatgact gaggtatggt cgtataatgc tgagctgttg	1260
gtggcaatgg aaaatcagca tacaatagat cttgctgact cagaaatgaa caaactttat	1320
gagcgtgtca gaaaacaact aagggagaat gctgaagaag atggaactgg atgttttgag	1380
atattccata agtgtgatga tcagtgcacg gagagcataa ggaacaacac ttatgacat	1440
actcaataga gaacagagtc attgcagaat agaatacaga tagaccagc gaaattgagt	1500
agtggataca aagacataat cttatggttt agcttcgggg catcatgttt tcttcttcta	1560
gccgtttaa tgggattggt tttcatttgc ataaagaatg gaaacatgcg gtgcaccatt	1620
tgtatataa	1629

&lt;210&gt; SEQ ID NO 12

&lt;211&gt; LENGTH: 1773

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Influenza A Virus

&lt;400&gt; SEQUENCE: 12

agcaaaagca ggggttatac catagacaac caaaggcaag acaatggcca tcatttatct	60
aattcttctg ttcacagcag tgagagggga ccaaatatgc attggatacc attccaacaa	120
ttccacagaa aaggttgaca caatcctaga gagaaatgac actgtgactc acgctgagga	180
cattcttgag aagactcaca atgggaagtt atgcaaaact aatggaatcc ctccacttga	240
attaagggat tgcagcattg ccggatggct ccttgggaat ccagaatgtg atatacttct	300
aactgtgcca gaatggatc acataataga aaaagaaaat ccaaggaacg gcttgtgcta	360
cccaggcagc ttcaatgatt atgaagaatt gaagcatctt atcagcagcg tgacacattt	420
tgagaaagta aagattctgc ccagaaatga atggacacag catacaacaa ctggagggtc	480
acaggcctgc gcagactatg gtggctcgtc attcttccgg aacatggtct ggttgacaaa	540
gaaagggctg aattatccaa ttgccaaaag atcttacaac aatacaagtg gggaacaaat	600
gctgatcatt tgggggatac atcaccocaa tgatgaaagt gaacaaagag cattgtatca	660
gaatgtgggg acctatgtgt cagtaggaac atcaaacctg aacaaaagat catccccaga	720
aatagcaaca agacctaaag tgaatggaca aggaggcaga atggaattct cgtggactat	780
cttagatata tgggacacaa taaattttga gactactggc aatctaattg caccagaata	840
tggtttcaaa atatccaaac gaggtagttc agggatcatg aaaacagaag gaaaacttga	900
aaactgcgag accaagtgc aaactcctt gggagcaata aatacaacat taccctttca	960
caatatccac ccaactgacca ttgggtgagt ccccaaatat gtaaaatcgg aaagattagt	1020
cttagcaaca ggactaagaa acgtccctca gattgagtca aggggattgt ttggggcaat	1080

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agctgggttt atagaggggtg gatggcaagg aatggttgat ggttggatg ggtatcatca 1140
cagcaatgac cagggatctg ggtatgcagc agacaaagaa tccactcaaa aggcaattga 1200
tggaatcacc aacaaggtaa attctgtgat cgaaaagatg aacaccaat tcggagctgt 1260
tgaaaaagaa ttcagtaact tggagagaag actggagaac ttgaataaaa agatggagga 1320
cggatttcta gatgtgtgga catacaatgc cgagctccta gttctaattg aaaatgagag 1380
gacacttgac tttcatgatt ctaatgtcaa gaatctatat gataaagtca gaatgcaact 1440
gagagacaat gcaaaagaac tagggaatgg atgttttgaa ttttatcaca aatgtgatga 1500
tgaatgcatg aacagtgtga agaatgggac atatgattat tccaagtatg aagaggagtc 1560
taaaactaac aggactgaaa tcaaaggggt taaattgagc aatatggggg tttatcaaat 1620
ccttgccatc tatgctacag tagcagggtc cctgtcactg gcaatcatga tagctgggat 1680
ttctatatgg atgtgctcca acgggtctct gcaatgcaga atctgcatat gatcatcagt 1740
cattttgtaa ttaaaaacac ccttgtttct act 1773

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<210> SEQ ID NO 13
<211> LENGTH: 1086
<212> TYPE: DNA
<213> ORGANISM: Influenza A Virus

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<400> SEQUENCE: 13

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caaaaacttc ccggaatga caacagcacg gcaacgctgt gccttgggca ccatgcagta 60
ccaaacggaa cgatagtgaa aacaatcacg aatgacaaa ttgaagtac taatgctact 120
gagctggtac agagtctctc aacagggtga atatgcgaca gtctcatca gatccttgat 180
ggagaaaact gcacactaat agatgctcta ttgggagacc ctcaagtgtga tggcttccaa 240
aataagaaat gggacctttt tgttgaacgc agcaaagcct acagcaactg ttacccttat 300
gatgtgccgg attatgctc ccttaggtca ctagtgcct catccggcac actggagttt 360
aacaatgaaa gcttcgattg gactggagtc actcagaatg gaacaagctc tgcttgcaaa 420
aggagatcta ataaaagttt ctttagtaga ttgaattggt tgaccactt aaaatacaaa 480
taccagcat tgaacgtgac tatgccaaac aatgaaaaat ttgacaaatt gtacatttgg 540
ggggttcacc acccgggtac ggacagtgac caaatcagcc tatatgctca agcatcagga 600
agaatcacag tctctaccaa aagaagccaa caaactgtaa tcccgaatat cggatctaga 660
cccagggtaa gggatgtctc cagccgaata agcatctatt ggacaatagt aaaaccggga 720
gacatacttt tgattaacag cacaggaat ctaattgctc ctccgggtta cttcaaaata 780
cgaaatggga aaagctcaat aatgagatca gatgcacca ttggcaaatg caattccgaa 840
tgcatcactc caaatggaag cattcccaat gacaaacctt ttcaaaatgt aaacaggatc 900
acatatgggg cctgtcccag atatgttaag caaaacactc tgaattggc aacagggatg 960
cgaaatgtac cagagaaaaca aactagaggc atatttggcg caatcgcggg tttcatagaa 1020
aatggttggg agggaatggt ggacggttgg tacggtttca ggcatacaaa ttctgagggc 1080
acagga 1086

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<210> SEQ ID NO 14
<211> LENGTH: 1048
<212> TYPE: DNA
<213> ORGANISM: Influenza A Virus

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<400> SEQUENCE: 14

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atgctatcaa tcacgattct gtttctgctc atagcagagg gttcctctca gaattacaca	60
gggaatcccg tgatattgctt gggacatcat gccgtatcca atgggacaat ggtgaaaacc	120
ctgactgatg accaagtaga agttgtcact gcccaagaat tagtggaatc gcaacatcta	180
ccggagtgtg gtcttagccc ttttaagatta gtagatggac aaacttgtga catcgtcaat	240
ggtgccttgg ggagtcagg ctgtgatcac ttgaatgggt cagaatggga tgtcttcata	300
gaacgaccca ctgctgtgga cacttggtat ccatttgatg tgccggatta ccagagccta	360
cggagtatcc tagcaaaaca tgggaaattt gagttcattg ctgaggaatt ccaatggaac	420
acagtcaaac aaaatgggaa atccggagca tgcaaaagag caaatgtgaa tgactttttc	480
aacagattga actggctgac caaatctgat gggaaatgcat acccacttca aaacctgaca	540
aaggtaaca acggggacta tgcaagactt tacatatggg gagttcatca tccttcaact	600
gacacagaac aaaccaactt gtataagaac aacctggga gagtaactgt ttccacaaa	660
accagtcaaa caagtgtggt accaaacatt ggcagtagac catgggtaag aggccaaagc	720
ggcaggatta gcttctattg gacaattgtg gagccaggag acctcatagt cttcaacacc	780
ataggaatt taattgtccc gagaggatcat tacaagctta acagtcaaaa gaagagcaca	840
attctgaata ctgcaattcc cataggatct tgtgttagta aatgtcacac agataggggt	900
tcaatctcta caacaaaacc ctttcagaac atctcaagaa tatcaattgg ggactgtccc	960
aagtatgtca aacagggatc cttgaaacta gctacaggaa tgaggaatat ccctgagaaa	1020
gcaaccagag gcctgttttg tgcaattg	1048

&lt;210&gt; SEQ ID NO 15

&lt;211&gt; LENGTH: 1707

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Influenza A Virus

&lt;400&gt; SEQUENCE: 15

atggagaaaa tagtgcttct tcttgcaata gtcagtcttg ttaaaagtga tcagatttgc	60
attggttacc atgcaaaaca ctgcacagag caggttgaca caataatgga aaagaacggt	120
actgttacac atgcccaaga catactggaa aagacacaca acgggaaact ctgcatcta	180
gatggagtga agcctctaatt tttgagagat tgtagtgtag ctggatggct cctcggaaac	240
cctatgtgtg acgaattcat caatgtgccg gaatggtctt acatagtgga gaaggccagt	300
ccagccaatg acctctgtta cccaggggat ttcaacgact atgaagaact gaaacaccta	360
ttgagcagaa taaaccactt tgagaaaatt cagatcatcc ccaaaagttc ttggtccaat	420
catgaagcct catcaggggt gagcgcagca tgtccatacc atgggaagcc ctctttttc	480
agaaatgtgg tatggcttat caaaaagaac agtgcatacc caacaataaa gaggagctac	540
aataatacca accaagaaga tcttttggtg ctgtggggga ttcaccatcc taatgatgcy	600
gcagagcaga caaagctcta tcaaaaacca accacatata tttccgttgg aacatcaaca	660
ctaaaccaga gattggtccc aaaaatagct actagatcca aagtaaacgg gcaaagtgga	720
agaatggagt tcttctggac aattttaaag ccgaatgatg ccataaattt cgagagtaat	780
ggaaatttca ttgctccaga atatgcatac aaaattgtca agaaagggga ctcagcaatt	840
atgaaaagtg aattggaata tggttaactgc aacaccaagt gtcaaaactcc aatgggggcy	900
ataaactcta gtatgccatt ccacaacata caccctctca caatcgggga atgccccaaa	960
tatgtgaaat caaacagatt agtccttgcg actggactca gaaatacccc tcaaagagat	1020
agaagaagaa aaaagagagg actatttga gctatagcag gttttataga gggagatgg	1080

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caaggaatgg tagatggttg gtaggggtac caccatagca atgagcaggg gagtggatac	1140
gctgcagaca aagaatccac tcaaaaggca atagatggag tcaccaataa ggtcaactcg	1200
atcattgaca aaatgaacac tcagtttgag gccgttgaa ggaatttaa taacttagaa	1260
aggaggatag aaaatttaaa caagaagatg gaagacggat tcctagatgt ctggacttat	1320
aatgctgaac ttctggttct catggaaaat gagagaactc tagactttca tgattcaaat	1380
gtcaagaacc tttacaacaa ggtccgacta cagcttaggg ataatgcaa ggagctgggt	1440
aatggtgtt tcgagttota tcacaaatgt gataatgaat gtatggaaag tgtaaaaaac	1500
gggacgtatg actaccgcga gtattcagaa gaagcaagac taaacagaga ggaaataagt	1560
ggagtaaaat tggaatcaat gggaaactac caaatactgt caatttattc aacagtggcg	1620
agttccctag cactggcaat catggtagct ggtctatctt tatggatgtg ctccaatggg	1680
tcggtacaat gcagaatttg catttaa	1707

&lt;210&gt; SEQ ID NO 16

&lt;211&gt; LENGTH: 1050

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Influenza A Virus

&lt;400&gt; SEQUENCE: 16

atgattgcaa tcattgtaat agcgatactg gcagcagccg gaaagtcaga caagatctgc	60
attgggtatc atgccaacaa ttcaacaaca caggtggata cgatacttga gaagaatgta	120
accgtcacac actcagttga attgctggag aatcagaagg aagaagatt ctgcaagatc	180
ttgaacaagg cccctctoga cctaaaggga tgcaccatag agggttggat cttggggaaat	240
ccccaatgag atctgttctg ttgtgaccaa agctgggtcat atatagtgga aagacctact	300
gccccaaatg ggatattgcta cccaggagct ttgaatgagg tagaagaact gaaagcattt	360
atcggatcag gagaaggggt agagagattt gagatgttcc ccaaaagcac atgggcaggg	420
gtagacacca gcagtgggggt aacaaaagct tgtccttata atagtggttc atctttctac	480
agaaacctcc tatggataat aaagaccaag tcagcagcgt atccagtaat taagggaaact	540
tacagcaaca ctggaaaacca gccaatctc tatttctggg gtgtgcacca tctcctgac	600
accaatgagc aaaatactct gtatggctct gccgatcggg atgttaggat gggaaactgag	660
agcatgaatt ttgccaagag cccagaaatt gcggcaagac ccgctgtgaa tggccaaaga	720
ggtcgaattg attattactg gtctgtttta aaaccaggag aaaccttgaa tgtggaatct	780
aatggaaatc taatcgctcc ttggtatgca tacaatttg tcaacacaaa taataagggga	840
gccgtcttca agtcaaatcc accaatcgag aattgcatg ccacatgcca gactattgca	900
ggagtcctaa ggaccaataa aacatttcag aatgtgagcc ctctgtggat aggagaatgc	960
cccaagtatg tgaaaagtga aagtctaagg cttgctactg gactaagaaa tgttccacag	1020
attgaaacca gagggctttt cggagctatc	1050

&lt;210&gt; SEQ ID NO 17

&lt;211&gt; LENGTH: 1698

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Influenza A Virus

&lt;400&gt; SEQUENCE: 17

atggaaaaat tcatcgcaat agcaaccttg gcgagcacia atgcatacga taggatatgc	60
attgggtacc aatcaaacaa ctccacagac acagtgaaca ctctcataga acagaatgta	120

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ccagtcaccc aaacaatgga gctcgtggaa acagagaaac atccccctta ttgtaacact	180
gatttaggtg ccccatgga actgcgagac tgcaagattg aggcagtaat ctatgggaac	240
cccaagtgtg acatccatct gaaggatcaa ggttggtcat acatagtgga gaggccacg	300
gcaccagaag ggatgtgtta ccttggatct gtggaaaatc tagaagaact gaggtttgtc	360
ttctccagtg ctgcatctta caagagaata agactatttg actattccag gtggaatgtg	420
actagatctg gaacgagtaa agcatgcaat gcatcaacag gtggccaatc cttctatag	480
agcatcaatt ggttgaccaa aaaggaacca gacacttatg acttcaatga aggagcttat	540
gttaataatg aagatggaga catcattttc ttatggggga tccatcatcc gccggacaca	600
aaagagcaga caacactata taaaaatgca aacactttga gtagtgttac tactaacact	660
ataaacagaa gctttcaacc aaatattggt cccagacat tagtaagagg acagcaaggg	720
aggatggatt actattgggg cattctgaaa agaggggaga ctctgaagat caggaccaac	780
ggaaatttaa tcgcacctga atttggctat ctgctcaaag gtgaaagcta cggcagaata	840
attcaaatg aggatatacc catcgggaac tgtaacacaa aatgtcaaac atatgcggga	900
gcaatcaata gcagcaaac ctttcagaat gcaagtaggc attacatggg agaatgtccc	960
aaatatgtga agaaggcaag cttgcgactt gcagttgggc ttaggaatac gccttctgtt	1020
gaaccagag gactgtttgg agccattgct ggtttcattg aaggaggatg gtctggaatg	1080
attgatgggt ggtatggatt tcacacagc aattcagagg gaacaggaat gccagctgac	1140
cagaaatcaa cacaagaagc catcgataag atcaccaata aagtcaacaa tatagttgac	1200
aagatgaaca gggagtttga agttgtgaat catgagttct ctgaagtga aaaaagaata	1260
aacatgataa acgataaaat agatgaccaa attgaagatc tttgggctta caatgcagag	1320
ctcctgtgc tcttagagaa ccagaaaacg ctagaogaac atgattccaa tgtcaaaaac	1380
ctttttgatg aagtgaaaag gagactgtca gccaatgcaa tagatgctgg gaacggttgc	1440
tttgacatac ttcacaaatg cgacaatgag tgtatggaaa ctataaagaa cggaaacttac	1500
gatcataagg aatatgaaga ggaggctaaa ctagaagga gcaagataaa tggagtaaaa	1560
ctagaagaga acaccactta caaaattctt agcatttaca gtacagtggc ggccagtctt	1620
tgcttgcaa tcctgattgc tggaggttta atcctgggca tgcaaatgg atctttaga	1680
tgcatgttct gtatttga	1698

&lt;210&gt; SEQ ID NO 18

&lt;211&gt; LENGTH: 1363

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Influenza A Virus

&lt;400&gt; SEQUENCE: 18

atggaaacag tactactaat gactatacta ctagtagcaa cagcaagcaa tgcagacaaa	60
atctgcatcg gccaccagtc aacaaaactc acagaaactg tggacacgct aacagaaacc	120
aatgttctg tgacacatgc caagaattg ctccacacag agcacaatgg aatgctgtgt	180
gcaacaaatc tgggacatcc cctaacttta gacacgtgca ctattgaagg actgatctat	240
ggtaaccctt cttgtgactt gctgttggga ggaagagaat ggctctacat cgtcgaag	300
tcacagctg taaatggaac gtgttaccct gggaaatgtag agaacctaga ggaactcagg	360
acacttttta gttecgctag ttectaccga agaatoocaa tcttoccaga cacaatctgg	420
aatgtgactt aactggaac aagcaagca tgttcagatt cattctacag gagtatgaga	480
tggctgactc aaaaaagcgg gtcttaccct gttcaagacg ctcaatacac aaataatag	540

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ggaaagagca	ttcttttctgt	gtggggcata	catcaccac	cactgaagc	tgacagaca	600
aattgtaca	caagaaccga	cacaacaaca	agcgtgaca	cagaagactt	aataggatc	660
ttcaaacga	tggtagggcc	aaggccoctt	gtcaatggc	tgacgggaag	aattaattat	720
tattggtcg	tactaaaacc	aggccagaca	ctgcgagtaa	gatccaatgg	gaatctaatt	780
gctccatggt	atggacacat	tctttcggga	gggagccatg	gaagaatcct	gaagactgat	840
ttaaaagta	gtaattcgt	agtgcaatgt	cagactgaaa	aaggcggctt	aaacagtaca	900
ttgccgttcc	acaatatcag	taaatatgca	tttgaaaact	gtcccaata	tgtagagtt	960
aaaagtctca	aactggcagt	agggttgagg	aacgtgcctg	ctagatcaag	tagaggacta	1020
ttcggagcca	tagctggatt	catagaagga	ggttgccag	gactagtcgc	tggttggtat	1080
ggtttccagc	attcaaatga	tcaaggggtt	ggtattgcg	cagatagga	ttcaactca	1140
aaggcaattg	atagaataac	aaccaagtg	aataatatag	tcgacaaaat	gaacaaaca	1200
tatgaaataa	ttgatcatga	attcagtgag	gttgaaacta	ggctcaacat	gatcaataat	1260
aagattgatg	accaaataca	agacatatgg	gcataaatg	cagagttgct	agtactactt	1320
gaaaaccaga	aaacactcga	tgagcatgac	gcaaatgtga	aga		1363

&lt;210&gt; SEQ ID NO 19

&lt;211&gt; LENGTH: 1727

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Influenza A Virus

&lt;400&gt; SEQUENCE: 19

agcaaaagca	ggggtcacaa	tgtacaaagt	agtagtaata	attgcgctcc	ttggagcagt	60
gaaaggtctt	gacagaatct	gcctaggaca	ccatgoggtt	gccaatggaa	ccattgtgaa	120
gacccttaca	aatgaacaag	aggaagtgac	caatgctact	gagacggtag	agagcacaaa	180
tttgaataaa	ttgtgtatga	aaggaagaag	ctacaaggac	ttgggcaatt	gtcaccoggt	240
aggaatgttg	ataggaacac	ctgtttgtga	tccgcacttg	accgggacct	gggacactct	300
cattgagcga	gagaatgcc	ttgcccactg	ttatccaggg	gcaaccataa	atgaagaagc	360
attgaggcag	aaaataatgg	aaagtggagg	aatcagcaag	atgagcactg	gcttcaacta	420
tgggtcttcc	atcacctcag	ctgggaccac	taaggcatgc	atgagaaatg	gaggagatag	480
tttctatgca	gagctcaaat	ggctagtgtc	aaagacaaag	ggacaaaatt	tccctcagac	540
aacaaacacc	tatcggaata	cggacacagc	agaacatctc	ataatatggg	gaattcatca	600
cccttcagc	acacaggaaa	agaatgactt	atcgggaact	cagtcaactat	ctatatcagt	660
tgagagttct	acatatcaga	acaactttgt	tccagttgtt	ggggcaagac	ctcaggtcaa	720
tgacaaaagt	gggcgaattg	actttcactg	gacactagta	cagccgggtg	acaacataac	780
cttctcagac	aatggaggtc	taatagcacc	aagtcgagtt	agcaaatata	ctggaagggg	840
tttgggaatc	caatcagaag	cggtgataga	caacagttgt	gaatccaaat	gcttttgag	900
agggggttct	ataaatacaa	agtcacctt	tcaaaatctg	tcaccagaa	cagtaggtca	960
atgccccaaa	tacgtaaatc	agaggagttt	actgcttga	acagggatga	ggaatgtgcc	1020
agaagtgtg	caggaaggg	gtctgtttgg	tgcaatagca	gggttcagag	aaaacggatg	1080
ggaaggaatg	gtagacggct	ggtatggtt	cagacaccaa	aatgccagc	gcacaggcca	1140
agctgctgat	tacaagagta	ctcaagcagc	tattgaccaa	atcacaggga	aactgaacag	1200
gttgattgag	aagaccaaca	ctgagtttga	gtcaatagaa	tctgaattca	gtgagactga	1260

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gcatcaaatt ggtaacgtca ttaattggac caaagattca ataaccgaca ttggactta	1320
caacgcagag ctattagtgg caatggagaa tcagcacaca attgacatgg ctgattcaga	1380
gatgctaaat ctgtatgaaa gggtaagaaa gcaactcaga cagaatgcag aagaagacgg	1440
aaagggatgt tttgagatat atcatacttg tgatgattcg tgcattggaga gtataaggaa	1500
caatacttat gaccattcac aatacagaga ggaggctctt ctgaatagac tgaacatcaa	1560
cccagtgaaa ctttcttcgg ggtacaaaga catcatactt tggtttagct tcggggaatc	1620
atgctttggt cttctagccg ttgttatggg tcttgttttc ttctgcctga aaaatggaaa	1680
catgcatgac acaatctgta tttagttaaa aacaccttgt ttctact	1727

&lt;210&gt; SEQ ID NO 20

&lt;211&gt; LENGTH: 1698

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Influenza A Virus

&lt;400&gt; SEQUENCE: 20

atggagaaaa cactgctatt tgcagctatt ttcctttgtg tgaagcaga tgagatctgt	60
atcgggtatt taagcaacaa ctgcacagac aaagttgaca caataatga gaacaatgtc	120
acggctacta gctcagtgga actgggtgag acagaacaca ctggatcatt ctgttcaatc	180
aatggaaaac aaccaataag ccttgagat tgttcatttg ctggatggat attagaaaac	240
cctatgtgtg atgaactaat tggaaagact tcatggtctt acattgtgga aaaaccaat	300
ccaacaaatg gaatctgtta cccaggaact ttagagagtg aagaagaact aagactgaaa	360
ttcagtggag ttttagaatt taacaaatc gaagtattca catcaaatgg atgggggtgct	420
gtaaattcag gagtaggagt aaccgctgca tgcaaatcg ggggttctaa ttctttcttt	480
cgaaacatgg tatggctgat acaccaatca ggaacatata ctgtaataaa gagaaccttt	540
aacaacacca aagggagaga tgtactgatt gtttgggaa ttcacatcc tgctacactg	600
acagaacatc aagatctgta taaaaaggac agctcctatg tagcagtggg ttcagagacc	660
tacaacagaa gattcactcc agaaatcaac actaggccca gagtcaatgg acaggccgga	720
cggatgacat tctactggaa gatagtcaaa ccaggagaat caataacatt cgaatcta	780
ggggcggtcc tagctcctag atatgctttt gagattgtct ctgttggaaa tgggaaactg	840
ttcaggagcg aactgaacat tgaatcatgc tctaccaaat gtcaaacaga aataggagga	900
attaatacga acaaaagctt ccacaatgtt cacagaaaca ctatcgggga ttgocccaag	960
tatgtgaatg tcaaatcctt aaagcttgca acaggaccta gaaatgtccc agcaatagca	1020
tcgagaggct tgtttgagc aatagctgga ttcataagaag ggggatggcc tggactgatc	1080
aatggatggg atgggttcca acacaggac gaagaaggaa caggcattgc agcagacaag	1140
gagtcaactc aaaaggcaat agaccagata acatccaagg taaataacat cgttgacagg	1200
atgaatacaa actttgagtc tgtgcaacac gaattcagtg aaatagagga aagaataaat	1260
caattatcaa aacacgtaga tgattctgtg gttgacatct ggtcatataa tgcacagctt	1320
ctcgttttac ttgaaaatga gaagacactg gacctccatg actcaaatgt caggaaacctc	1380
catgagaaa gtcagaagaat gctaaaggac aatgccaaag atgaggggaa cggatgcttc	1440
accttttacc ataagtgtga caataaatgc attgaacgag ttagaaacgg aacatgatgat	1500
cataaagaat tcgaggagga atcaaaaaatc aatcgccagg agattgaagg ggtgaaacta	1560
gattctagtg ggaatgtgta taaaactctg tcaatttaca gctgcattgc aagcagctctt	1620
gtattggcag cactcatcat ggggttcatg ttttgggcat gcagtaatgg atcatgtaga	1680

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 tgtaccatth gcatttag 1698

<210> SEQ ID NO 21  
 <211> LENGTH: 1695  
 <212> TYPE: DNA  
 <213> ORGANISM: Influenza A Virus

<400> SEQUENCE: 21

atgaaaaat tcatactttt gagtactgtc ttggcagcaa gctttgcata tgacaaaatt 60  
 tgcattggat accaaacaaa caactcgact gaaacggtaa acacactaag tgaacaaaac 120  
 gttccggatga cgcagggtga agaacttga catcgtggga ttgatccgat cctgtgtgga 180  
 acggaactag gatcaccact agtgcttgat gactgttcat tagagggctt aatcctaggc 240  
 aatcccaaat gtgatcttta tttgaatgac agggaatggt catacatagt agagaggccc 300  
 aaagagatgg aaggagtgtg ctatccaggg tcaattgaaa accaggaaga gctaagatct 360  
 ctgttttctt ccatcaaaaa atatgaaaga gtgaagatgt ttgatttcac caaatggaat 420  
 gtcacataca ctgggaccag caaggcctgc aataatacat caaaccaagg ctctattctat 480  
 aggagcatga gatggttgac cttaaaatca ggacaatttc cagtccaaac agatgagtac 540  
 aagaacacca gagattcaga cattgtattc acctgggcca ttcaccacc accaacatct 600  
 gatgaacaag taaaattata caaaaatcct gatactctct cttcagtcac caccgtagaa 660  
 atcaatagga gcttcaagcc taatataggg ccaagaccac tcgtgagagg acaacaaggg 720  
 agaatggatt actactgggc tgttcttaaa cctggacaaa cagtcaaaa acaaaccaat 780  
 ggtaatctta ttgcacctga atatggtcac ttaatcacag ggaaatcaca tggcaggata 840  
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 atgaacacaa gcaaaccttt ccagaacact agtaagcact atattgggaa atgccccaaa 960  
 tacataccat cagggagttt aaaattggca atagggtcca ggaatgtccc acaagttcaa 1020  
 gatcgggggc tctttggagc aattgcaggc ttcataagaag gcgatggcc agggctagtg 1080  
 gctggttggc acggtattca gcatcaaaa cgggagggga caggcatagc tgcagacaga 1140  
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 atgattaatt ccaaaattga tgatcagata actgacatat gggcatacaa tgctgaattg 1320  
 cttgtcctat tggaaaatca gaagacatta gatgagcatg acgctaattg aaggaatcta 1380  
 catgatcggg tcagaagagt cctgagggaa aatgcaattg acacaggaga cggtgcttt 1440  
 gagattttac ataaatgtga caacaattgt atggacacga ttagaaacgg gacatacaat 1500  
 cacaagagat atgaggaaga aagcaaaatc gaacgacaga aagtcaatgg tgtgaaactt 1560  
 gaggagaatt ctacatataa aattctgagc atctacagca gtgttgctc aagcttagtt 1620  
 ctactgctca tgattattgg gggtttcatt ttcgggtgtc aaaatggaaa tgttcgttgt 1680  
 actttctgta tttaa 1695

<210> SEQ ID NO 22  
 <211> LENGTH: 1701  
 <212> TYPE: DNA  
 <213> ORGANISM: Influenza A Virus

<400> SEQUENCE: 22

atggctctaa atgtcattgc aactttgaca cttataagtg tatgtgtaca tgcagacaga 60

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atatgcgtgg ggtatctgag caccaattca tcagaaaggg tgcacacgct ccttgaaaat	120
ggggtocccag tcaccagctc cattgatctg attgagacaa accacacagg aacatactgt	180
tctctaaatg gagtcagtc agtgcatttg ggagattgca gctttgaagg atggattgta	240
ggaaaccag cctgcaccag caactttggg atcagagagt ggtcatacct gattgaggac	300
cccgcggccc ctcatgggct ttgctaccct ggagaattaa acaacaatgg tgaactcaga	360
cacttgttca gtggaatcag gtcattcagt agaacggaat tgatcccacc tacctcctgg	420
ggggaagtac ttgacggtac aacatctgct tgcagagata acacgggaac caacagcttc	480
tatcgaaatt tagtttggtt tataaagaag aatactagat atccagttat cagtaagacc	540
tacaacaata caacgggaag ggatgttcta gttttatggg gaatacatca cccagtgtct	600
gtggatgaga caaagactct gtatgtcaat agtgatecat acacactggt ttccaccaag	660
tcttgagcgc agaaatataa actagaaacg ggagtccgac ctggctataa tggacagagg	720
agctggatga aaattttattg gctcttgata catccagggg agatgattac tttcgagagt	780
aatggtggat ttttagcccc aagatatggg tacataattg aagaatatgg aaaaggaagg	840
atthttccaga gtcgcatcag aatgtctagg tgcaacacca agtgccagac ttcggttgga	900
gggataaaca caaacagaac gttccaaaac atcgataaga atgctcttgg tgactgtccc	960
aaatacataa agtctggcca actcaageta gccactggac tcagaaatgt gccagctata	1020
tcgaatagag gattgttcgg agcaattgca gggttcatag aaggaggctg gccaggttta	1080
atcaatggtt ggtacggttt tcagcatcaa aatgaacagg gaacaggaat agctgcagac	1140
aaagaatcaa cacagaaagc tatagaccag ataacaacca aaataaataa cattattgat	1200
aaaatgaatg ggaactatga ttcaattagg ggtgaattca atcaagtga gaagcgtata	1260
aacatgcttg cagacagaat agatgatgcc gtgacggaca tttggtcata caatgccaaa	1320
cttcttgtat tgctggaaaa tgataaaact ttgatatgc atgatgctaa tgtaagaat	1380
ttacatgagc aagtacgaag agaattgaag gacaatgcaa ttgacgaagg aaatggctgt	1440
tttgaactcc ttcataaatg caatgactcc tgcattgaaa ctataagaaa tggaaactgt	1500
gaccacactg agtatgcaga ggagtcaaag ttaagaggc aagaatcga tgggatcaaa	1560
ctcaaatcag aagacaacgt ttcaaaagca ttatcaatat acagttgcat tgcaagtagt	1620
gttgactag taggactcat actctcttcc atcatgtggg cctgtagtag tgggaattgc	1680
cgattcaatg tttgtatata a	1701

&lt;210&gt; SEQ ID NO 23

&lt;211&gt; LENGTH: 1749

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Influenza A Virus

&lt;400&gt; SEQUENCE: 23

agcaaaagca ggggaaaaatg attgcactca tattgggtgc actggctctg agccacactg	60
cttattctca gatcacaat gggacaacag gaaaccccat tatatgcttg gggcatcatg	120
cagtggaaaa cggcacatct gttaaaacac taacagacaa tcacgtagaa gttgtgtcag	180
ctaaagaatt agttgagacg aaccacactg atgaactgtg cccaagcccc ttgaagcttg	240
tcgacgggca agactgccac ctcatcaatg gtgcattggg gagtccagggc tgtgaccggt	300
tgcaggacac cacttgggat gtcttcattg aaaggccccc tgcagtagac acatgttate	360
cattcgacgt cccagattac cagagtctca gaagcatcct agcaagcagt gggagtttgg	420
agttcatcgc cgaacaattc acctggaatg gtgtcaaagt tgacggatca agcagtgctt	480

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gtttgagggg	cggtcgcaac	agcttcttct	cccgactaaa	ctggctaacc	aaagcaacaa	540
atggaacta	tggacctatt	aacgtcacta	aagaaaatac	gggctcttat	gtcaggctct	600
atctctgggg	agtgcacac	ccatcaagcg	ataatgagca	aacggatctc	tacaaggtag	660
caacagggag	agtaacagta	tctaccgct	cggaacaaat	cagtattgtt	cccaatatag	720
gaagtagacc	gagggttaagg	aatcagagcg	gcaggataag	catctactgg	accctagtaa	780
accagggga	ctccatcatt	ttcaacagta	ttgggaattt	gattgcacca	agaggccact	840
acaaaataag	caaatctact	aagagcacag	tgcttaaaag	tgacaaaagg	attgggtcat	900
gcacaagccc	ttgcttaact	gataaagggt	cgatccaaag	tgacaaacct	ttcagaatg	960
tatcaaggat	tgctatagga	aactgcccga	aatatgtaa	gcaaggggcc	ctgatgttag	1020
caactggaat	gcgcaacatc	cctggcaaac	aggcaagggg	cttatttggg	gcaattgctg	1080
gattcattga	aaatggttgg	caaggcctga	ttgatgggtg	gtatggattc	aggcaccaaa	1140
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tagatgtcac	agactccgaa	atgaacaagc	tttttgaag	agtaagaagg	caattaagag	1440
agaatgcaga	agatcaaggc	aacggttgtt	tcgagatatt	ccatcagtgt	gacaacaatt	1500
gtatagaaag	cattagaaac	ggaacttatg	accacaacat	ctacagggat	gaagccatca	1560
acaatcgaat	caaaaataat	cctgtcactt	tgacgatggg	gtacaaggac	ataatcctgt	1620
ggatttcttt	ctccatgtca	tgctttgtct	tcgtggcact	gattctggga	tttgttctat	1680
gggcttgtca	aaacgggaat	atccgatgcc	aaatctgtat	ataaagaaaa	aacacccttg	1740
tttctactc						1749

&lt;210&gt; SEQ ID NO 24

&lt;211&gt; LENGTH: 1762

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Influenza A Virus

&lt;400&gt; SEQUENCE: 24

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tcgatgggtg	gatctgacaa	gatttgtctc	gggcaccatg	ccgtagcaaa	tgggacaaaa	120
gtcaacacac	taactgagaa	aggagtggaa	gtggtcaatg	ccacggagac	agtggagatt	180
acaggaataa	ataaagtgtg	cacaaaaggg	aagaaagcgg	tggacttggg	atcttgtgga	240
atactgggaa	ctatcattgg	gcctccacaa	tgtagactctc	atcttaaat	caaagctgat	300
ctgataatag	aaagaagaaa	ttcaagtgc	atctgttacc	cagggaatt	cactaatgag	360
gaagcactga	gacaaataat	cagagaatct	ggtggaattg	acaagagcc	aatgggattt	420
agatattcag	gaataaaaac	agacggggca	accagtgcgt	gtaagagaac	agtgtcctct	480
ttctactcag	aatgaaatg	gcttttatcc	agcaaggcta	accaggtgtt	cccacaactg	540
aatcagacat	acaggaacaa	cagaaaagaa	ccagccctaa	ttgtttgggg	agtacatcat	600
tcaagtctct	tggatgagca	aaataagcta	tatggagctg	ggaacaagct	gataacagta	660
ggaagctcaa	aataccaaca	atcgttttca	ccaagtccag	gggacaggcc	caaagtgaat	720
ggtcaggccg	ggaggatcga	ctttcattgg	atgctattgg	accagggga	tacagtcact	780

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tttaccttca atggtgcatt catagcccca gatagagcca cctttctccg ctctaattgcc	840
ccatcggggag ttgagtacaa tgggaagtca ctgggaatac agagtgatgc acaaattgat	900
gaatcatgtg aaggggaatg cttctacagt ggagggacaa taaacagccc tttgccattt	960
caaaacatcg atagttgggc tgcggaagg tgccccagat atgtaaagca atcaagcctg	1020
ccgctggcct taggaatgaa aatgtacca gagaaaatac atactagggg actggtcgggt	1080
gcaattgcag gattcatoga gaatggatgg gaaggactca ttgatggatg gtatggattt	1140
aggcatcaaa atgcacaggg gcaggaaca gctgctgact acaagagtac tcaggctgca	1200
attgaccaga taacagggaa acttaataga ttaattgaaa aaaccaacac acagtttgaa	1260
ctcatagaca atgagttcac tgaagtggag cagcagatag gcaatgtaat aaactggaca	1320
agggactcct tgactgagat ctggctacac aatgctgaac ttctagtagc aatggaaaat	1380
cagcatacaa ttgacctgac agattctgaa atgaacaaac tctatgagag agtgagaaga	1440
cagctaaggg agaatgccga ggaggatgga actggatggt ttgagatttt ccaccgatgt	1500
gacgatcaat gtatggagag catacgaaat aatacttaca atcacactga atatcgacag	1560
gaagccttac agaataggat aatgatcaat ccggtaaagc ttagtggtgg gtacaaagat	1620
gtgatactat ggttttagctt cggggcatca tgtgtaatgc ttctagccat tgctatgggt	1680
cttattttca tgtgtgtgaa aaacgggaat ctgctgtgca ctatctgtat ataattattt	1740
gaaaaacacc cttgtttcta ct	1762

&lt;210&gt; SEQ ID NO 25

&lt;211&gt; LENGTH: 1760

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Influenza A Virus

&lt;400&gt; SEQUENCE: 25

agcaaaagca ggggatattg tcaaaacaac agaatggtga tcaaagtgct ctactttctc	60
atcgatttgt taagtaggta ttcgaaagca gacaaaatat gcataggata tctaagcaac	120
aacgccacag acacagtaga cacactgaca gagaacggag ttccagtgac cagctcagtt	180
gatctcgttg aaacaaacca cacaggaaca tactgctcac tgaatggaat cagccaatt	240
catcttggtg actgcagctt tgagggatgg atcgtaggaa acccttctctg tgccaaccaac	300
atcaacatca gagagtggtc gtatctaatt gaggacccca atgccccca caaactctgc	360
ttcccaggag agttagataa taatggagaa ttacgacatc tcttcagcgg agtgaactct	420
tttagcagaa cagaattaat aagtcccaac aaatggggag acattctgga tggagtcacc	480
gcttcttgcc gcgataatgg ggcaagcagt ttttacagaa atttggtctg gatagtgaag	540
aataaaaatg gaaaataccc tgcataaag ggggattaca ataacacaac aggcagagat	600
gttctagtac tctggggcat tcaccatccg gatacagaaa caacagccat aaacttgtag	660
gcaagcaaaa acccctacac attagatca acaaaggaat ggagcaaaag atatgaacta	720
gaaattggca ccagaatagg tgatggacag agaagtggga tgaaactata ttggcacctc	780
atgcgccctg gagagaggat aatgtttgaa agcaacgggg gccttatagc gccagatac	840
ggatacatca ttgagaagta cggtacagga cgaattttcc aaagtggagt gagaatggcc	900
aatgcaaca caaagtgtca aacatcatta ggtgggataa acaccaaca aactttccaa	960
aacatagaga gaaatgctct tggagattgc ccaaagtaca taaagtctgg acagctgaag	1020
cttgcaactg ggctgagaaa tgtcccatcc gttggtgaaa gaggtttggt tgggtcaatt	1080
gcaggcttca tagaaggagg gtggcctggg ctaattaatg gatggtatgg tttccagcat	1140

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cagaatgaac aggggactgg cattgctgca gacaaagcct ccaactcagaa agcgatagat	1200
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agaggggaat tcaatcaagt agaaaagagg atcaacatgc tcgctgatcg agttgatgat	1320
gcagtaactg acatatggtc gtacaatgct aaacttcttg tactgcttga aaatgggaga	1380
acattggact tacacgacgc aaatgtcagg aacttacacg atcagggtcaa gagaatattg	1440
aaaagtaatg ctattgatga aggagatggt tgcttcaatc ttcttcacaa atgtaatgac	1500
tcatgcatgg aaactattag aaatgggacc tacaatcatg aagattacag ggaagaatca	1560
caactgaaaa ggcaggaaat tgagggaaata aaattgaagt ctgaagacaa tgtgtataaa	1620
gtactgtcga tttatagctg cattgcaagc agtattgtgc tggtaggtct catacttgcg	1680
ttcataatgt gggcatgcag caatggaaat tgccgggtta atgtttgtat atagtcggaa	1740
aaaaaccct tgtttctact	1760

&lt;210&gt; SEQ ID NO 26

&lt;211&gt; LENGTH: 1882

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Influenza A Virus

&lt;400&gt; SEQUENCE: 26

agcagaagcg ttgcatttcc taatatccac aaaatgaagg caataattgt actactcatg	60
gtagtaacat ccaatgcaga tcgaatctgc actgggataa catcgtcaaa ctcacctcat	120
gtggttaaaa ctgccactca aggggaagtc aatgtgactg gtgtgatacc actaacaaca	180
acacctacca aatctcattt tgcaaatctc aaaggaacac agaccagagg aaaactatgc	240
ccaaactggt ttaactgcac agatctggac gtggccctag gcagaccaa atgcatgggg	300
aacacacctc ccgcaaaagt ctcaactctc catgaagtca aacctgctac atctggatgc	360
tttctataa tgcacgacag aacaaaaatc agacaactac ctaatcttct cagaggatat	420
gaaaacatca gggtatcaac cagtaatggt atcaatacag agacggcacc aggaggacc	480
tacaagtggt ggacctcagg atcttgccct aacgttgcta atgggaacgg cttcttcaac	540
acaatggctt ggggtatccc aaaagacaac aacaagacag caataaatcc agtaacagta	600
gaagtacat acatttgctc agaaggggaa gaccaaatta ctgtttgggg gttccactct	660
gatgacaaaa cccaatgga aagactctat ggagactcaa atcctcaaaa gttccactca	720
tctgccaatg gagtaaccac acattatggt tctcagattg gtggcttccc aatcaaaaca	780
gaagacgaag ggctaaaaca aagcggcaga attgtgtgtg attacatggt acaaaaacct	840
ggaaaaacag gaacaattgt ttatcaaaaga ggcattttat tgcctcaaaa agtgtggtgc	900
gcaatggca ggagcaaggt aataaaaggg tccttgctt taattggtga agcagattgc	960
ctccacgaaa agtacggtgg attaaataaa agcaagcctt actacacagg agagcatgca	1020
aaggccatag gaaattgccc aatattgggtg aaaacacct tgaagctggc caatggaacc	1080
aaatatagac cgctgcaaa actattaaag gaaagaggtt tcttcggagc tattgctggt	1140
ttcttgaag gaggatggga aggaatgatt gcaggttggc acggatacac atctcatgga	1200
gcacatggag tggcagtggc agcagacctt aagagtacac aagaagctat aaacaagata	1260
acaaaaaatc tcaactatct aagttagcta gaagtaaaaa accttcaaag actaagcgga	1320
gcaatgaatg agcttcacga cgaaatactc gagctagacg aaaaagtgga tgatctaaga	1380
gctgatacaa taagctcaca aatagagctt gcagtcttgc tttccaacga agggataata	1440

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aacagtgaag atgagcatct cttggcactt gaaagaaaaac tgaagaaaaat gcttggcccc	1500
tctgctgtag aaatagggaa tgggtgcttt gaaaccaaac acaaatgcaa ccagacttgc	1560
ctagacagga tagctgctgg cacctttaat gcaggagatt tttctcttc cacttttgat	1620
tcattaaaca ttactgctgc atctttaaat gatgatggct tggataatca tactatactg	1680
ctctactact caactgctgc ttctagcttg gctgtaacat taatgatagc tatcttcatt	1740
gtctacatgg tctccagaga caatgtttct tgttccatct gtctgtgagg gagattaagc	1800
cctgtgtttt cctttactgt agtgcctcatt tgcttgcac cattacaaag aaacgttatt	1860
gaaaaatgct cttgttacta ct	1882

&lt;210&gt; SEQ ID NO 27

&lt;211&gt; LENGTH: 2073

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Influenza A Virus

&lt;400&gt; SEQUENCE: 27

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gctgaaaaaa taaagatatg ccttcaaaag caagtgaaca gtagcttcag cctacacaat	120
ggcttcggag gaaatttcta tgccacagaa gaaaaagaa tgtttgagct tgttaagccc	180
aaagctggag cctctgtctt gaatcaaagt acatggattg gctttggaga ttcaaggact	240
gacaaaagca attcagcttt tcctaggtct gctgatgttt cagcaaaaac tgctgataag	300
ttctgttttt tgtctggtgg atccttaaat ttgagtatgt ttggcccacc tgggaaggta	360
gactaccttt accaaggatg tggaaaacat aaagtttttt atgaaggagt taactggagt	420
ccacatgctg ctataaattg ttacagaaaa aattggactg atatcaaact gaatttcag	480
aaaaacattt atgaattggc ttacacaatca cattgcata gcttgggtgaa tgccttggac	540
aaaactattc ctttacaagt gactgctggg actgcaggaa attgcaacaa cagcttctta	600
aaaaatccag cattgtacac acaagaagtc aagccttcag aaaacaaatg tgggaaagaa	660
aatcttgctt tcttcacact tccaacccaa tttggaacct atgagtgcaa actgcatctt	720
gtggcttctt gctatttcat ctatgatagt aaagaagtgt acaataaaag aggatgtgac	780
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gtatcacctt acacagggaa ttctggagac accccaacaa tgcaatgtga catgctccag	900
ctgaaacctg gaagatattc agtaagaagc tctccaagat tccttttaat gcctgaaaga	960
agttattgct ttgacatgaa agaaaaagga ccagtcactg ctgtccaatc catttgggga	1020
aaaggcagag aatctgacta tgcagtggat caagcttgct tgagcactcc aggggtgcatg	1080
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cctttggctg caaaggaaga atccattcca aaaatccag atggccttct aattcccacc	1320
agtggaaccg ataccactgt aaccaaacct aagagcagaa tttttggaat cgatgaacctc	1380
attattgggt tgctccttgt tgcaatcgtt gaacacaggaa tggaggctta tctgcttgg	1440
agtagaaaag aatcaggagg aggtgtgaca aaagaatcag ctgaaaaagg gtttgagaaa	1500
attgaaaatg acatacaaat tttaaaatct tctataaata tcgcaataga aaaactaaat	1560
gacagaatth ctcatgatga gcaagccatc agagatctaa ctttagaaat tgaaaatgca	1620
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agcataggat tacaggaatc tttatgggaa ctagcttcag aaataacaaa tagagcagga 1740
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agctgtcaaa attttatttt caagttcaac gaaactgcac ctgttccaac cattccccct 1860
cttgacacaa aaattgatct gcaatcagat cctttttact ggggaagcag cttgggctta 1920
gcaataactg ctactatttc attggcagct ttggtgatct ctgggatcgc catctgcaga 1980
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tttataaaaa acaaaaatcc ccttgctact gct 2073

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&lt;210&gt; SEQ ID NO 28

&lt;211&gt; LENGTH: 1670

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Influenza Virus

&lt;400&gt; SEQUENCE: 28

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agatcttcgc tgacacaata tgtataggct accatgccaa caactcaacc gacactgttg 60
acacagtact tgagaagaat gtgacagtga cacactctgt caacctactt gaggacagtc 120
acaatggaaa actatgtcta ctaaaaggaa tagcccccact acaattgggt aattgcagcg 180
tgccgggatg gatcttagga aaccagaat gcgaattact gatttccaag gaatcatggt 240
cctacattgt agaaacacca aatcctgaga atggaacatg ttaccagggt tatttcgccg 300
actatgagga actgagggag caattgagtt cagtatcttc atttgagaga ttcgaaatat 360
tccccaaaga aagctcatgg cccaaccaca ccgtaaccgg agtatcagca tcatgctccc 420
ataatgggaa aagcagtttt tacagaaatt tgctatggct gacggggaag aatggtttgt 480
acccaaacct gagcaagtcc tatgtaaaca acaaagagaa agaagtcctt gtactatggg 540
gtgttcacca cccgcctaac ataggggaacc aaagggcact ctatcataca gaaaatgctt 600
atgtctctgt agtgtcttca cattatagca gaagattcac ccagaaata gccaaaagac 660
ccaaagtaag agatcaggaa ggaagaatca actactactg gactctgctg gaacctgggg 720
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tcacaatagg agagtgtcca aagtatgtca ggagtgcaaa attaaggatg gttacaggac 960
taaggaaat cccatccatt caatccagag gttgttttg agccattgcc ggtttcattg 1020
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gatctggcta tgctgcagat caaaaaagta cacaaaatgc cattaacggg attacaaca 1140
aggtcaatc tgtaattgag aaaatgaaca ctcaattcac agctgtgggc aaagagttca 1200
acaaattgga aagaagatg gaaaactta ataaaaagt tgatgatggg tttctagaca 1260
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agaaaattga tggagtgaat ttggaatcaa tgggagtata ccagattctg gcgatctact 1560
caactgtcgc cagttccctg gttcttttgg tctccctggg ggcaatcagc ttctggatgt 1620
gttccaatgg gtctttgcag tgtagaatat gcatetaaga gctcaggcct 1670

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<210> SEQ ID NO 29  
 <211> LENGTH: 32  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Primer  
  
 <400> SEQUENCE: 29  
  
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<210> SEQ ID NO 30  
 <211> LENGTH: 46  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Primer  
  
 <400> SEQUENCE: 30  
  
 aatagagctc cattttctct caagatgatt aattaattaa ttagtc 46

<210> SEQ ID NO 31  
 <211> LENGTH: 46  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Primer  
  
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<210> SEQ ID NO 32  
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 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Primer  
  
 <400> SEQUENCE: 32  
  
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<210> SEQ ID NO 33  
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 <212> TYPE: DNA  
 <213> ORGANISM: Influenza Virus  
  
 <400> SEQUENCE: 33  
  
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 gtgacagtga cacactctgt caacctactt gaggacagtc acaatggaaa actatgtcta 180  
 ctaaaaggaa tagccccact acaattgggt aattgcagcg ttgccgatg gatccttagga 240  
 aaccagaat gcgaattact gatttccaag gaatcatggt cctacattgt agaaacacca 300  
 aatcctgaga atggaacatg ttaccagggt tatttcgccc actatgagga actgaggagg 360  
 caattgagtt cagtatcttc atttgagaga ttcgaaatat tccccaaaga aagctcatgg 420  
 cccaaccaca ccgtaaccgg agtatcagca tcatgtctcc ataatgggaa aagcagtttt 480  
 tacagaaatt tgctatggct gacggggaag aatggttgt acccaaacct gagcaagtcc 540  
 tatgtaaaca acaagagaa agaagtctt gtactatggg gtgttcatca cccgcctaac 600  
 ataggggaacc aaaggccct ctatcataca gaaaatgctt atgtctctgt agtgtcttca 660  
 cattatagca gaagattcac ccagaata gccaaaagac ccaaagtaag agatcaggaa 720

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ggaagaatca actactactg gactctgctg gaacctgggg atacaataat atttgaggca 780
aatggaaatc taatagcgcc atggatgct tttgactga gtagaggctt tggatcagga 840
atcatcacct caaatgcacc aatggatgaa tgtgatgcga agtgtcaaac acctcagga 900
gctataaaca gcagctctcc tttccagaat gtacaccag tcacaatagg agagtgtcca 960
aagtatgtca ggagtgcaaa attaaggatg gttacaggac taaggaacat cccatccatt 1020
caatccagag gtttgtttgg agccattgcc ggtttcattg aaggggggtg gactggaatg 1080
gtagatgggt ggtatggta tcatcatcag aatgagcaag gatctggcta tgctgcagat 1140
caaaaaagta cacaaaatgc cattaacggg attacaaaca aggtgaattc tgtaattgag 1200
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gactatccaa aatattccga agaatcaaag ttaaacaggg agaaaattga tggagtgaaa 1560
ttggaatcaa tgggagtcta tcagattctg gcgatctact caactgtcgc cagttccctg 1620
gttcttttgg tctccctggg ggcaatcagc ttctggatgt gttccaatgg gtctttgcag 1680
tgtagaatat gcattctgaga ccagaatttc a 1711

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&lt;210&gt; SEQ ID NO 34

&lt;211&gt; LENGTH: 1781

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Medicago Sativa

&lt;400&gt; SEQUENCE: 34

```

ccaaatcctt aacattcttt caacaccaac aatggcgaaa aacgttgca ttttcggtt 60
attgttttct cttcttctgt tggttccttc tcagatcttc gctgaggaat catcaactga 120
cgctaaggaa tttgttctta cattggataa cactaatttc catgacactg ttaagaagca 180
cgatttcacg gtcgttgaat tctacgcacc ttgggtgtgga cactgtaaga agctagcccc 240
agagtatgag aaggctgctt ctatcttgag cactcacgag ccaccagttg ttttgctaa 300
agttgatgcc aatgaggagc acaacaaaga cctcgcatcg gaaaatgatg ttaagggatt 360
cccaaccatt aagattttta ggaatgggtg aaagaacatt caagaatata aaggtccccg 420
tgaagctgaa ggtattgttg agtattgaa aaaacaaagt ggccctgcat ccacagaaat 480
taaatctgct gatgatgcga ccgcttttgt tggtgacaac aaagtgtta ttgtcggagt 540
tttccctaaa ttttctgggt aggagtacga taacttcatt gcattagcag agaagttgcg 600
ttctgactat gactttgctc acactttgaa tgccaaacac cttccaaagg gagactcatc 660
agtgctctgg cctgtgggta ggttatttaa gccatttgac gagctctttg ttgactcaaa 720
ggatttcaat gtagaagctc tagagaaatt cattgaagaa tccagtaccc caattgtgac 780
tgtcttcaac aatgagccta gcaatcacc ttttgttctc aaattcttta actctcccaa 840
cgcaaaggct atgttgttca tcaactttac taccgaaggt gctgaatctt tcaaaaacaa 900
ataccatgaa gtggctgagc aatacaaca acagggagtt agctttcttg ttggagatgt 960
tgagtctagt caaggctcct tccagtattt tggactgaag gaagaacaag tacctctaat 1020
tattatctag cataatgatg gcaagaagtt tttcaaaccc aatttgaac ttgatcaact 1080

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cccaacttgg ttgaaggeat acaaggatgg caaggttgaa ccatttgta agtctgaacc 1140
tattcctgaa actaacaacg agcctgttaa agtgggtggt gggcaaacctc ttgaggacgt 1200
tgttttcaag tctgggaaga atgttttgat agagttttat gctccttggg gtggctactg 1260
caagcagttg gctccaatct tggatgaagt tgctgtctca ttccaaagcg atgctgatgt 1320
tgttattgca aaactggatg caactgocaa cgatatccca accgacacct ttgatgtcca 1380
aggctatcca accttgactc tcaggtcagc aagtggaaaa ctatcacaat acgacgggtg 1440
taggacaaaag gaagacatca tagaattcat tgaaaagaac aaggataaaa ctgggtgctgc 1500
tcatcaagaa gtagaacacac caaaagctgc tgctcagcca gaagcagaac aacccaaaaga 1560
tgagctttga aaagtccgcg ttggaggata tcggcacaca gtcactctgcg ggctttacaa 1620
ctcttttgta tctcagaatc agaagttagg aaatcttagt gccaatctat ctatttttgc 1680
gtttcatttt atctttttgg tttactctaa tgtattactg aataatgtga gttttggcgg 1740
agtttagtac tggaaactttt gtttctgtaa aaaaaaaaaa a 1781

```

&lt;210&gt; SEQ ID NO 35

&lt;211&gt; LENGTH: 1027

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Influenza Virus

&lt;400&gt; SEQUENCE: 35

```

agcgaagca ggtagatatt gaaagatgag tcttctaacc gaggtcgaaa cgtacgttct 60
ctctatcacc cgtcaggcc cctcacaagc cgagatcgca cagagacttg aagatgtctt 120
tgcagggaag aacaccgatc ttgaggttct catggaatgg ctaaagacaa gaccaatcct 180
gtcacctctg actaagggga ttttaggatt tgtgttcacg ctcaccgtgc ccagtgagcg 240
aggactgcag cgtagacgct ttgtccaaaa tgcccttaat gggaaacgggg atccaaataa 300
catggacaaa gcagttaaac tgtataggaa gctcaagagg gagataacat tccatggggc 360
caaagaaatc tcaactcagtt attctgctgg tgcacttgcc agttgtatgg gcctcatata 420
caacaggatg ggggctgtga ccaactgaagt ggcatttggc ctggtatgtg caacctgtga 480
acagattgct gactcccagc atcggctca taggcaaatg gtgacaacaa ccaaccact 540
aatcagacat gagaacagaa tggttttagc cagcactaca gctaaggcta tggagcaaat 600
ggctggatcg agtgagcaag cagcagagc catggagggt gctagtcagg ctaggcaaat 660
ggtgcaagcg atgagaacca ttgggactca tcctagctcc agtgctggtc tgaaaaatga 720
tcttctgaa aatttgcagg cctatcagaa acgaatgggg gtgcagatgc aacggttcaa 780
gtgatcctct cgetattgcc gcaaatatca ttgggatctt gcaactgata ttgtggatc 840
ttgatcgtct ttttttcaaa tgcatttacc gtcgctttaa atacggactg aaaggagggc 900
cttctacgga aggagtcca aagtctatga gggaagaata tcgaaaggaa cagcagagtg 960
ctgtggatgc tgacgatggt cattttgtca gcatagagct ggagtaaaaa actaccttgt 1020
ttctact 1027

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&lt;210&gt; SEQ ID NO 36

&lt;211&gt; LENGTH: 1788

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Clone

&lt;400&gt; SEQUENCE: 36

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cactttgtga gtctacactt tgattccctt caaacacata caaagagaag agactaatta 60

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attaattaat catcttgaga gaaaatgaaa gtaaaactac tggctctggt atgcacattt 120
acagctacat atgcagacac aatatgtata ggctaccatg ctaacaactc gaccgacact 180
gttgacacag tacttgaaaa gaatgtgaca gtgacacact ctgtcaacct gcttgagaac 240
agtcacaatg gaaaactatg tctattaaaa ggaatagccc cactacaatt gggtaattgc 300
agcgttgccg ggtggatctt aggaaacca gaatgogaat tactgatttc caaggagtca 360
tggctctaca ttgtagaaaa accaaatcct gagaatggaa catgttacct agggcatttc 420
gctgactatg aggaactgag ggagcaattg agttcagtat cttcatttga gaggttcgaa 480
atattcccca aagaaagctc atggcccaac cacaccgtaa cgggagtgtc agcatcatgc 540
tcccataatg gggaaagcag tttttacaga aatttgctat ggctgacggg gaagaatggt 600
ttgtacccaa acctgagcaa gtcctatgca aacaacaaag aaaaagaagt ccttgacta 660
tggggtgttc atcaccgcc aaacataggt gaccaaagg ccctctatca tacagaaaat 720
gcttatgtct ctgtagtgtc ttcacattat agcagaaaat tcaccccaga aatagccaaa 780
agacccaaag taagagatca agaaggaaga atcaattact actggactct gcttgaacct 840
ggggatacaa taatatttga ggcaaatgga aatctaatag cgccaagata tgctttcgca 900
ctgagttagag gctttggatc aggaatcctc aactcaaatg caccaatgga taaatgtgat 960
gogaagtgcc aaacacctca gggagctata aacagcagtc ttcctttcca gaacgtacac 1020
ccagtcacaa taggagagtg tccaaagtat gtcaggagtg caaaattaag gatggttaca 1080
ggactaagga acatcccctc cattcaatcc agaggtttgt ttggagccat tgcggtttc 1140
attgaagggg ggtggactgg aatggtagat ggttggtatg gttatcatca tcagaatgag 1200
caaggatctg gctatgctgc agatcaaaaa agcacacaaa atgccattaa tgggattaca 1260
aacaaggtca attctgtaat tgagaaaatg aacactcaat tcacagcagt gggcaaagag 1320
ttcaacaaat tggaaagaag gatggaaaac ttgaataaaa aagttgatga tgggtttata 1380
gacatttggg catataatgc agaactggtg gttctactgg aaaatgaaag gactttggat 1440
ttccatgact ccaatgtgaa gaatctgtat gagaaaagta aaagccagtt aaagaataat 1500
gctaaagaaa taggaaatgg ggtttttgag ttctatcaca agtgtaacga tgaatgcatg 1560
gagagtgtaa agaatggaac ttatgactat ccaaaatatt ccgaagaatc aaagttaaac 1620
agggagaaaa ttgatggagt gaaattggaa tcaatgggag tctatcagat tctggcgatc 1680
tactcaacag tcgccagttc tctggttctt ttggtctccc tgggggcaat cagcttctgg 1740
atgtgttcca atgggtcttt acagtgtaga atatgcatct aagagctc 1788

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&lt;210&gt; SEQ ID NO 37

&lt;211&gt; LENGTH: 1788

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Clone

&lt;400&gt; SEQUENCE: 37

```

cactttgtga gtctacactt tgattccctt caaacacata caaagagaag agactaatta 60
attaattaat catcttgaga gaaaatgaaa gtaaaactac tggctctggt atgcacattt 120
acagctacat atgcagacac aatatgtata ggctaccatg ccaacaactc aaccgacact 180
gttgacacag tacttgagaa gaatgtgaca gtgacacact ctgtcaacct gcttgaggac 240
agtcacaatg gaaaattatg tctattaaaa ggaatagccc cactacaatt gggtaattgc 300

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agcgttgccg gatggatcct aggaaaccca gaatgcgaat tactgatttc cagggaatca 360
tggctcctaca ttgtagaaaa accaaatcct gagaatggaa catgttacc caggcatttc 420
gccgactatg aggaactgag ggagcaattg agttcagtat cttcatttga gagattogaa 480
atattcccca aagaaagctc atggcccaac cacaccacaa cgggagtatc agcatcatgc 540
tcccataatg gggaaagcag tttttacaaa aatttgctat ggctgacggg gaagaatggt 600
ttgtacccaa acctgagcaa gtcctatgca aacaacaaag agaagaagt cctgttacta 660
tgggggtgtc atcacccgcc taacataggt gaccaaaggg ctctctatca taaagaaaat 720
gcttatgtct ctgtagtgtc ttcacattat agcagaaaaat tcaccccaga aatagccaaa 780
agacccaaag taagagatca agaaggaaga atcaactact actggactct acttgaacce 840
ggggatacaa taatatttga ggcaaatgga aatctaatag cgccaagata tgctttcgca 900
ctgagtagag gctttggatc aggaatcacc aactcaaatg caccaatgga tgaatgtgat 960
gogaagtgcc aaacacctca gggagctata aacagcagtc ttcctttcca gaatgtacac 1020
cctgtcacia taggagagtg tccaaagtat gtcaggagtg caaaattaag gatggttaca 1080
ggactaagga acatcccacc cattcaatcc agaggtttgt ttggagccat tgccggtttc 1140
attgaagggg ggtggactgg aatggtagat ggttggtatg gttatcatca tcagaatgag 1200
caaggatctg gctatgctgc agatcaaaaa agcacacaaa atgccattaa tgggattaca 1260
aacaaggtca attctgtaat tgagaaaaatg aacactcaat tcacagctgt gggcaaaagag 1320
ttcaacaaat tggaaagaag gatggaaaac ttaaataaaa aagttgatga tgggtttata 1380
gacatttggg catataatgc agaattggtg gttctactgg aaaatgaaag gactttggat 1440
ttccatgact ccaatgtgaa gaatctgtat gagaaagtaa aaagccaatt aaagaataat 1500
gccaaagaaa taggaaatgg gtgttttgag ttctatcata agtgtaacga tgaatgcatg 1560
gagagtgtaa aaaatggaac ttatgactat ccaaaaatatt ccgaagaatc aaagttaaac 1620
agggagaaaa ttgatggagt gaaattggaa tcaatgggag tctatcagat tctggcgatc 1680
tactcaacag tcgccagttc tctggttctt ttggtctccc tgggggcaat cagcttctgg 1740
atgtgttcca atgggtcttt gcagtgtaga atatgcatct gagagctc 1788

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&lt;210&gt; SEQ ID NO 38

&lt;211&gt; LENGTH: 1791

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Clone

&lt;400&gt; SEQUENCE: 38

```

cactttgtga gtctacactt tgattccctt caaacacata caaagagaag agactaatta 60
attaattaat catcttgaga gaaaatgaag actatcattg ctttgagcta cattctatgt 120
ctggttttca ctcaaaaact tcccggaat gacaacagca cggcaacgct gtgccttggg 180
caccatgcag taccaaacgg aacgatagtg aaaacaatca cgaatgacca aattgaagtt 240
actaatgcta ctgagctggg tcagagttcc tcaacaggtg aaatatgcga cagtcctcat 300
cagatccttg atggagaaaa ctgcacacta atagatgctc tattgggaga ccctcagttg 360
gatggcttcc aaaataagaa atggggacctt tttgttgaac gcagcaaagc ctacagcaac 420
tgttaccctt atgatgtgcc ggattatgcc tcccttaggt cactagtgtc ctcacccggc 480
aactggaggt ttaacaatga aagtttcaat tggactggag tcaactcaaaa cggaacaagc 540
tctgcttgca taaggagatc taataacagt ttctttagta gattgaattg gttgaccocac 600

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ttaaaattca aataccagc attgaacgtg actatgcca acaatgaaaa atttgacaaa	660
ttgtacattt ggggggttca ccaccgggt acggacaatg accaaatctt cctgtatgct	720
caagcatcag gaagaatcac agtctctacc aaaagaagcc aacaaactgt aatcccgaat	780
atcggatcta gaccagagt aaggaatata ccagcagaaa taagcatcta ttggacaata	840
gtaaaaccgg gagacatact ttgattaac agcacagga atctaattgc tcctaggggt	900
tacttcaaaa tacgaagtgg gaaaagctca ataatgagat cagatgcacc cattggcaaa	960
tgcaattctg aatgcatcac tccaaacgga agcattccca atgacaaaacc attccaaaat	1020
gtaaacagga tcacatacgg ggcctgtccc agatatgtta agcaaacac tctgaaattg	1080
gcaacagga tgcaaatgt accagagaaa caaactagag gcatatttgg cgcaatcgcg	1140
ggtttcatag aaaatggttg ggagggaatg gtggatggtt ggatggttt caggcatcaa	1200
aattctgagg gaataggaca agcagcagat ctcaaaagca ctcaagcagc aatcgatcaa	1260
atcaatggga agctgaatag gttgatcggg aaaaccaacg agaaattcca tcagattgaa	1320
aaagagttct cagaagtoga agggagaatc caggacctg agaaatatgt tgaggacacc	1380
aaaatagatc tctggtcata caacgcggag cttctgttg ccctggagaa ccaacataca	1440
attgatctaa ctgactcaga aatgaacaaa ctgtttgaaa aaacaaagaa gcaactgagg	1500
gaaaatgctg aggataggg caatggttgt ttcaaaatat accacaaatg tgacaatgcc	1560
tgcataggat caatcagaaa tggaaactat gaccacgatg tatacagaga tgaagcatta	1620
aacaaccggt tccagatcaa gggcgttgag ctgaagtcag gatacaaaga ttggatacta	1680
tggaattcct ttgccatata atgttttttg ctttgtgttg ctttgttggg gttcatcatg	1740
tgggcctgcc aaaaaggcaa cattaggtgc aacatttga tttgagagct c	1791

&lt;210&gt; SEQ ID NO 39

&lt;211&gt; LENGTH: 1791

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Clone

&lt;400&gt; SEQUENCE: 39

cactttgtga gtctacactt tgattccctt caaacacata caaagagaag agactaatta	60
attaattaat catcttgaga gaaaatgaag actatcattg ctttgagcta cattctatgt	120
ctggttttca ctcaaaaact tcccggaat gacaacagca cggcaacgct gtgccttggg	180
caccatgcag taccaaacgg aacgatagtg aaaacaatca cgaatgacca aattgaagtt	240
actaatgcta ctgagctggt tcagagttcc tcaacaggtg gaatatgca cagtcctcat	300
cagatccttg atggagaaaa ctgcacacta atagatgctc tattgggaga ccctcagtg	360
gatggcttcc aaaataagaa atgggacctt tttgttgaac gcagcaaagc ctacagcaac	420
tgttaccctt atgatgtgcc ggattatgcc tcccttaggt cactagtgtc ctcatcggc	480
acactggagt ttaacgatga aagtttcaat tggactggag tcaactcaaaa tggacaacagc	540
tctgcttgca aaaggagatc taataacagt ttcttttagta gattgaattg gttgaccac	600
ttaaaattca aataccagc attgaacgtg actatgcca acaatgaaaa atttgacaaa	660
ttgtacattt ggggggttca ccaccgggt acggacaatg accaaatctt cctgcatgct	720
caagcatcag gaagaatcac agtctctacc aaaagaagcc aacaaactgt aatcccgaat	780
atcggatcta gaccagaat aaggaatata ccagcagaaa taagcatcta ttggacaata	840

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gtaaaaccgg gagacatact tttgattaac agcacagggg atctaattgc tcttaggggt 900
tacttcaaaa tacgaagtgg gaaaagctca ataatgagat cagatgcacc cattggcaaa 960
tgcaattctg aatgcatcac tccaaatgga agcattccca atgacaaaacc atttcaaaat 1020
gtaaacagga tcacatatgg ggcctgtccc agatatgtta agcaaaacac tctgaaattg 1080
gcaacagggg tgcgaaatgt accagagaaa caaactagag gcatatttgg cgcaatcgcg 1140
ggtttcatag aaaatggttg ggaggggaatg gtggatggtt ggtacggttt caggcatcaa 1200
aattctgagg gaataggaca agcagcagat ctcaaaagca ctcaagcagc aatcaatcaa 1260
atcaatggga agctgaatag gttgatcggg aaaaccaacg agaaattcca tcagattgaa 1320
aaagagttct cagaagtaga agggagaatc caggacctcg agaaatatgt tgaggacact 1380
aaaatagatc tctggtcata caacgcggag cttctgttg ccttgagaaa ccaacataca 1440
attgatctaa ctgactcaga aatgaacaaa ctgtttgaaa gaacaaaaga gcaactgagg 1500
gaaaatgctg aggatatggg caatggttgt ttcaaaatat accacaaatg tgacaatgcc 1560
tgcataggat caatcagaaa tggaaactat gaccatgatg tatacagaga tgaagcatta 1620
aacaaccggg tccagatcaa aggcgttgag ctgaagtcag gatacaaaga ttggatacta 1680
tggatttctt ttgccatata atgttttttg ctttgtgttg ctttgttggg gttcatcatg 1740
tgggcctgcc aaaaaggcaa cattaggtgc aacatttgca tttgagagct c 1791

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&lt;210&gt; SEQ ID NO 40

&lt;211&gt; LENGTH: 1848

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Clone

&lt;400&gt; SEQUENCE: 40

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cactttgtga gtctacactt tgattccctt caaacacata caaagagaag agactaatta 60
attaattaat catcttgaga gaaaatgaag gcaataattg tactactcat ggtagtaaca 120
tccaatgcag atcgaatctg cactgggata acatcgtcaa actcaccaca tgttgtaaaa 180
actgctactc aaggggaggt caatgtgact ggtgtaatac cactgacaac aacaccacc 240
aaatctcatt ttgcaaatct caaaggaaca gaaaccagag ggaaactatg cccaaaatgc 300
ctcaactgca cagatctgga cgtggccttg ggcagaccaa aatgcacggg gaacataccc 360
tcggcaagag tttcaatact ccatgaagtc agacctgtta catctgggtg ctttcctata 420
atgcacgaca gaacaaaaat tagacagctg cctaaacttc tcagaggata cgaacatatc 480
aggttatcaa ctcataacgt tatcaatgca gaaaatgcac caggaggacc ctacaaaatt 540
ggaacctcag ggtcttgccc taacgttacc aatggaaacg gatTTTTgc aacaatggct 600
tgggcccgtcc caaaaaacga caacaacaaa acagcaacaa attcattaac aatagaagta 660
ccatacattt gtacagaagg agaagaccaa attaccgttt ggggggttcca ctctgataac 720
gaaaccctaaa tggcaaaagt ctatggggac tcaaagcccc agaagttcac ctcatctgcc 780
aacggagtga ccacacatta cgtttcacag attggtggct tcccaaatca aacagaagac 840
ggaggactac cacaaagcgg tagaattgtt gttgattaca tgggtgcaaaa atctgggaaa 900
acaggaacaa ttacctatca aagaggtatt ttattgcctc aaaaagtgtg gtgcgcaagt 960
ggcaggagca aggtataaaa aggatcgttg cctttaattg gagaagcaga ttgcctccac 1020
gaaaaatacg gtggattaaa caaaagcaag ccttactaca caggggaaca tgcaaaaggcc 1080
ataggaaatt gcccaatgat ggtgaaaaca cccttgaagc tggccaatgg aaccaaatat 1140

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agacctctg caaaactatt aaaggaaagg ggtttcttcg gagctattgc tggtttctta 1200
gaaggaggat gggaaaggaat gattgcaggt tggcacggat acacatccca tggggcacat 1260
ggagtagcgg tggcagcaga ccttaagagc actcaagagg ccataaacia gataacaaaa 1320
aatctcaact ctttgagtga gctggaagta aagaatcttc aaagactaag cggtgccatg 1380
gatgaactcc acaacgaaat actagaacta gacgagaaaag tggatgatct cagagctgat 1440
acaataagct cacaaataga actcgcagtc ctgctttcca atgaaggaat aataaacagt 1500
gaagatgagc atctcttggc gcttgaaga aagctgaaga aaatgctggg cccctctgct 1560
gtagagatag ggaatggatg ctttgaacc aaacacaagt gcaaccagac ctgtctcgac 1620
agaatagctg ctggtacctt tgatgcagga gaattttctc tccccacttt tgattcactg 1680
aatattactg ctgcatcttt aaatgacgat ggattggata atcatactat actgctttac 1740
tactcaactg ctgcctccag tttggctgta acattgatga tagctatctt tgttgtttat 1800
atggtctcca gagacaatgt ttcttgctcc atctgtctat aagagctc 1848

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&lt;210&gt; SEQ ID NO 41

&lt;211&gt; LENGTH: 1845

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Clone

&lt;400&gt; SEQUENCE: 41

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cactttgtga gtctacactt tgattccctt caaacacata caaagagaag agactaatta 60
attaattaat catcttgaga gaaaatgaag gcaataattg tactactcat ggtagtaaca 120
tccaatgcag atcgaatctg cactggaata acatcttcaa actcacctca tgtggtcaaa 180
acagccactc aaggggaggt caatgtgact ggtgtgatac cactaacaac aacaccaaca 240
aaatcttatt ttgcaaatct caaaggaaca aggaccagag ggaaactatg cccagactgt 300
ctcaactgca cagatctgga tgtggctttg ggcagaccaa tgtgtgtggg gaccacacct 360
tcggcgaagg cttcaatact ccacgaagtc aaacctgta catccgggtg ctttcctata 420
atgcacgaca gaacaaaaat caggcaacta cccaatcttc tcagaggata tgaaaatate 480
aggctatcaa cccaaaacgt catcgatgag gaaaaggcac caggaggacc ctacagactt 540
ggaacctcag gatcttgccc taacgctacc agtaagagcg gatTTTTgc aacaatggct 600
tgggtgtgoc caaaggacaa caacaaaaat gcaacgaacc cactaacagt agaagtacca 660
tacatttgta cagaagggga agaccaaate actgtttggg ggttccattc agataacaaa 720
accCAAatga agaacctcta tggagactca aatcctcaaa agttcacctc atctgctaat 780
ggagtaacca cacactatgt ttctcagatt ggcagcttcc cagatcaaac agaagacgga 840
ggactaccac aaagcggcag gattgttgtt gattacatga tgcaaaaacc tgggaaaaca 900
ggaacaattg tctaccaaag aggtgttttg ttgcctcaaa aggtgtgggtg cgcgagtggc 960
aggagcaaaag taataaaaagg gtccttgctt ttaattgggtg aagcagattg ctttcatgaa 1020
aaatacggty gattaaacaa aagcaagcct tactacacag gagaacatgc aaaagccata 1080
ggaaattgcc caatatgggt gaaaacacct ttgaagctcg ccaatggaac caaatataga 1140
cctcctgcaa aactatataa gaaaaggggt ttcttcggag ctattgctgg tttcctagaa 1200
ggaggatggg aaggaatgat tgcaggctgg cacggataca catctcaggg agcacatgga 1260
gtggcagtyg cggcggacct taagagtaag caagaagcta taaacaagat acaaaaaaat 1320

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ctcaattctt tgagtgagct agaagtaaag aatcttcaaa gactaagtgg tgccatggat	1380
gaactocaca acgaaatact cgagctggat gagaagtgg atgatctcag agctgacact	1440
ataagctcgc aaatagaact tgcagtcttg ctttccaacg aaggaataat aaacagtgaa	1500
gatgagcatc tattggcact tgagagaaaa ctaaagaaaa tgctgggtcc ctctgctgta	1560
gagataggaa atggatgctt cgaacccaaa cacaagtgca accagacctg cttagacagg	1620
atagctgctg gcacctttaa tgcaggagaa ttttctctcc ccacttttga ttcactgaac	1680
attactgctg catctttaa tgatgatgga ttgataacc atactatact gctctattac	1740
tcaactgctg cttctagttt ggctgtaaca ttgatgctag ctatttttat tgtttatatg	1800
gtctccagag acaacgtttc atgctccatc tgtctataag agctc	1845

<210> SEQ ID NO 42  
 <211> LENGTH: 1779  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Clone

<400> SEQUENCE: 42

cactttgtga gtctacactt tgattccctt caaacacata caaagagaag agactaatta	60
attaattaat catcttgaga gaaatggcc atcatttacc taattctcct gttcacagca	120
gtgagagggg accaaatgat cattggatac catgccaata attccacaga gaaggtcgac	180
acaattctag agcggaaagt cactgtgact catgccaagg acattcttga gaagacctat	240
aacggaaagt tatgcaaaact aaacggaatc cctccacttg aactagggga ctgtagcatt	300
gccgatggc tccttggaag tccagaatgt gataggcttc taagtgtgcc agaatggctc	360
tatataatgg agaagaaaaa cccgagagac ggtttgtggt atccaggcag cttcaatgat	420
tatgaagaat tgaacatct cctcagcagc gtgaaacatt tcgagaaagt aaagattctg	480
cccaaagata gatggacaca gcatacaaca actggaggtt cacgggectg cgcgggtgct	540
ggtaatccat cattcttcag gaacatggtc tggctgacaa agaagaatc aaattatccg	600
gttgccaaag gatcgtacaa caatacaagc ggagaacaaa tgctaataat ttggggggtg	660
caccatccca atgatgagac agaacaaga acattgtacc agaatgtggg aacctatgtt	720
tccgtaggca catcaacatt gaacaaaagg tcaaccccag acatagcaac aaggcctaaa	780
gtgaatggac taggaagtag aatggagttc tcttgacccc tattggatat gtgggacacc	840
ataaattttg agagtactgg taatctaatt gcaccagagt atggattcaa aatatcgaaa	900
agaggtagtt cagggatcat gaaaacagaa ggaacacttg agaactgtga gaccaaatgc	960
caaactcctt tgggagcaat aaatacaaca ttgccttttc acaatgtcca cccactgaca	1020
ataggtgagt gccccaaata tgtaaaatcg gagaagttgg tcttagcaac aggactaagg	1080
aatgttcccc agattgaatc aagaggattg tttggggcaa tagctggttt tatagaagga	1140
ggatggcaag gaatggttga tggttggtat ggataaccatc acagcaatga ccagggatca	1200
gggatgagc cagacaaga atccactcaa aaggcatttg atggaatcac caacaaggta	1260
aattctgtga ttgaaaagat gaacacccaa tttgaagctg ttgggaaaga gttcagtaac	1320
ttagagagaa gactggagaa cttgaacaaa aagatggaag acgggtttct agatgtgtgg	1380
acatacaatg ctgagcttct agttctgatg gaaaatgaga ggacacttga ctttcatgat	1440
tctaattgca agaactctgta tgataaagtc agaatgcagc tgagagacaa cgtcaaagaa	1500
ctaggaaatg gatgttttga attttatcac aatgtgatg atgaaatgcat gaatagtgtg	1560

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aaaaacggga cgtatgatta tccaagtat gaagaagagt ctaaaactaaa tagaaatgaa 1620
atcaaagggg taaaattgag cagcatgggg gtttatcaaa tccttgccat ttatgctaca 1680
gtagcagggt ctctgtcact ggcaatcatg atggctggga tctctttctg gatgtgctcc 1740
aacgggtctc tgcagtgcag gatctgcata tgagagctc 1779

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<210> SEQ ID NO 43
<211> LENGTH: 1794
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Clone

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<400> SEQUENCE: 43

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cactttgtga gtctacactt tgattccctt caaacacata caaagagaag agactaatta 60
attaattaat catcttgaga gaaaatggag aaaatagtgc ttcttcttgc aatagtcagc 120
cttgtaaaaa gtgatcagat ttgcatctgg taccatgcaa acaactcgac agagcagggt 180
gacacaataa tggaaaagaa cgttactgtt acacatgccc aagacatact ggaaaagaca 240
cacaacggga agctctgcga tctagatgga gtgaagcctc tgattttaag agattgtagt 300
gtagctggat ggctcctcgg aaacccaatg tgtgacgagt tcatcaatgt gccggaatgg 360
tcttacatag tggagaaggc caaccagcc aatgacctct gttaccagc gaatttcaac 420
gactatgaag aactgaaaca cctattgagc agaataaacc attttgagaa aattcagatc 480
atccccaaaa gttcttggtc cgatcatgaa gcctcatcag gggtcagctc agcatgtcca 540
taccagggaa cgcctcctt tttcagaaat gtggtatggc ttatcaaaaa gaacaataca 600
taccacaaca taaagagaag ctacaataat accaaccagg aagatctttt gatactgtgg 660
gggattcatc attctaata tgcggcagag cagacaaagc tctatcaaaa cccaaccacc 720
tatatttccg ttgggacatc aacactaaac cagagattgg taccaaaaat agctactaga 780
tccaaagtaa acgggcaaag tggaggatg gatctctctt ggacaatttt aaaaccgaat 840
gatgcaatca acttcgagag taatggaaat ttcattgctc cagaatatgc atacaaaatt 900
gtcaagaaa gggactcagc aattgttaaa agtgaagtgg aatatggtaa ctgcaataca 960
aagtgtcaaa ctccaatagg ggcgataaac tctagatgac cattccacaa catacacctt 1020
ctcaccatcg gggaatgcc caaatatgtg aaatcaaaaca aatagtcct tcgactggg 1080
ctcagaaata gtctctaaag agaaaagaaga agaaaaagag gactatttgg agctatagca 1140
gggtttatag agggaggatg gcagggaatg gtagatgggt ggtatgggta ccaccatagc 1200
aatgagcagg ggagtgggta cgctgcagac aaagaatcca ctcaaaaggc aatagatgga 1260
gtcaccaata aggtcaactc gatcattgac aaaatgaaca ctcagtttga ggccgttgg 1320
agggaaatta ataacttaga aaggagaata gagaatttaa acaagaaaat ggaagacgga 1380
ttcctagatg tctggactta taatgctgaa cttctggttc tcatggaaaa tgagagaact 1440
ctagacttcc atgattcaaa tgtcaagaac ctttacgaca aggtccgact acagcttagg 1500
gataatgcaa aggagctggg taacggttgt ttcgagttct atcacaatg tgataatgaa 1560
tgtatgaaaa gtgtaagaaa cggaacgtat gactaccgc agtattcaga agaagcaaga 1620
ttaaaaagag aggaaataag tggagtataa ttggaatcaa taggaactta ccaaatctg 1680
tcaatttatt caacagttgc gagttctcta gcactggcaa tcatgggtggc tggctctatc 1740
ttgtggatgt gctccaatgg gtcggttaca tgcagaattt gcatttaaga gctc 1794

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<210> SEQ ID NO 44
<211> LENGTH: 1797
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Clone

<400> SEQUENCE: 44
cactttgtga gtctacactt tgattccctt caaacacata caaagagaag agactaatta    60
attaattaat catcttgaga gaaaatggag aaaatagtgc ttctttttgc aatagtcagt    120
cttgtaaaaa gtgatcagat ttgcattggt taccatgcaa acaactcgac agagcagggt    180
gacacaataa tggaaaagaa cgttactggt acacatgccc aagacatact ggaaaagaca    240
cacaatggga agctctgoga tctagatgga gtgaagcctc taattttgag agattgtagt    300
gtagctggat ggctcctcgg aaacccaatg tgtgacgagt tcatcaatgt gccggaatgg    360
tcttacatag tggagaaggc caatccagtc aatgacctct gttaccaggg ggatttcaat    420
gactatgaag aattgaaaca cctattgagc agaataaacc attttgagaa aattcagatc    480
atccccaaaa gttcttggtc cagtcatgaa gcctcattgg gggtcagctc agcatgtcca    540
taccagggaa agtctcctct tttcagaaat gtggtatggc ttatcaaaaa gaacagtaca    600
taccacaaca taaagaggag ctacaataat accaaccaag aagatctttt ggtactgtgg    660
gggattcacc atcctaataa tgcggcagag cagacaaagc tctatcaaaa cccaaccacc    720
tatatctcgg ttgggacatc tacactaaac cagagattgg taccaagaat agctactaga    780
tccaaagtaa acgggcaaag tggaaaggat gagttcttct ggacaatttt aaaaccgaat    840
gatgcaatca acttcgagag taatggaaat ttcattgctc cagaatatgc atacaaaatt    900
gtcaagaaag gggactcaac aattatgaaa agtgaattgg aatatggtaa ctgcaatacc    960
aagtgtcaaa ctccaatggg ggcgataaac tctagcatgc cattccacaa tatacacct    1020
ctcaccatcg gggaatgccc caaatatgtg aaatcaaaca gattagtctt tgcgactggg    1080
ctcagaaata gccctcaaag agagagaaga agaaaaaaga gaggattatt tggagctata    1140
gcaggtttta tagagggagg atggcagggg atggtagatg gttggtatgg gtaccaccat    1200
agcaacgagc aggggagtggt gtacgctgca gacaagaat ccaactcaaaa ggcaatagat    1260
ggagtcacca ataaggtaaa ctcgattatt gacaaaatga acaactcagtt tgaggccggt    1320
ggaagggaaat ttaacaactt agaaaggaga atagagaatt taaacaagaa gatggaagac    1380
gggtctctag atgtctggac ttataatgct gaacttctag ttctcatgga aaacgagaga    1440
actctagact ttcattgactc aaatgtcaag aacctttacg acaaggctcc actacagctt    1500
agggataatg caaaggagct gggtaacggg tgtttcagat tctatcataa atgtgataat    1560
gaatgtatgg aaagtgtaa gaaacggaac tatgactacc cgcagtattc agaagaagca    1620
agactaaaaa gagaggaaat aagtggagta aaattggaat caataggaat ttaccaataa    1680
ttgtcaatth attctacagt ggccagctcc cttagcactgg caatcatggt agctggtcta    1740
tccttatgga tgtgctccaa tgggtcgtta caatgcagaa tttgcattta agagctc    1797

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<210> SEQ ID NO 45
<211> LENGTH: 1791
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Clone

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<400> SEQUENCE: 45

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cactttgtga gtctacactt tgattccctt caaacacata caaagagaag agactaatta      60
attaattaat catcttgaga gaaaatgatt gcaatcattg taatagcaat actggcagca      120
gccgaaaagt cagacaagat ctgcattggg tatcatgcca acaattcaac aacacaggta      180
gatacgatagc ttgagaagaa tgtgactgtc acacactcaa ttgaattgct ggaaaatcag      240
aaggaagaaa gattctgcaa gatattgaac aaggccctc tcgacttaag ggaatgtacc      300
atagagggtt ggatcttggg gaatcccaa tgcgacctat tgcttggtga tcaaagctgg      360
tcatacattg tggaaagacc tactgtctaa aacgggatct gctaccagg aaccttaaat      420
gaggtagaag aactgagggc acttattgga tcaggagaaa gggtagagag atttgagatg      480
tttcccaaaa gcacctggca aggagttgac accaacagtg gaacaacaag atcctgcctt      540
tattctactg gtgcgtcttt ctacagaaac ctctatgga taataaaaac caagacagca      600
gaatatccag taattaaggg aatttacaac aacctggaa cccagccaat cctctatttc      660
tggggtgtgc atcatcctcc taacaccgac gagcaagata ctctgtatgg ctctggtgat      720
cgatacgtta gaatgggaaac tgaagcatg aattttgcca agagtccgga aattgcggca      780
aggcctgctg tgaatggaca aagaggcaga attgattatt attggtcggg tttaaaacca      840
ggggaacct tgaatgtgga atctaattgga aatctaactg ccccttggtg tgcatacaaa      900
tttgtcaaca caaatagtaa aggagcgtc ttcaggtcag atttaccat cgagaactgc      960
gatgccacat gccagactat tgcaggggtt ctaaggacca ataaaacatt tcagaatgtg     1020
agtcccctgt ggataggaga atgtcccaaa tacgtgaaaa gtgaaagtct gaggcttgca     1080
actggactaa gaaatgttcc acagattgaa actagaggac tcttcggagc tattgcaggg     1140
tttattgaag gaggatggac tgggatgata gatgggtggt atggctatca ccatgaaaat     1200
tctcaagggt caggatatgc agcagacaga gaaagcactc aaaaggctgt aaacagaatt     1260
acaaataagg tcaattccat catcaacaaa atgaacacac aanttgaagc tgtcgatcac     1320
gaattttcaa atctggagag gagaattgac aatctgaaca aaagaatgca agatggattt     1380
ctggatgttt ggacatacaa tgctgaactg ttggttcttc ttgaaaacga aagaacacta     1440
gacatgcatg acgcaaatgt gaagaacctc catgaaaagg tcaaatcaca actaagggac     1500
aatgctacga tcttagggaa tggttgcttt gaattttggc ataagtgtga caatgaatgc     1560
atagagtctg tcaaaaatgg tacatatgac tatcccaaat accagactga aagcaaatta     1620
aacaggctaa aaatagaatc agtaaagcta gagaaccttg gtgtgtatca aattcttgcc     1680
atztatagta cggtatcgag cagcctagtg ttggtagggc tgatcatggc aatgggtctt     1740
tggatgtgtt caaatggttc aatgcagtgc aggatatgta tataagagct c           1791

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&lt;210&gt; SEQ ID NO 46

&lt;211&gt; LENGTH: 1803

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Clone

&lt;400&gt; SEQUENCE: 46

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cactttgtga gtctacactt tgattccctt caaacacata caaagagaag agactaatta      60
attaattaat catcttgaga gaaaatgaa actcaaattc taatattagc cacttcggca      120
ttcttctatg tacgtgcaga taaaatctgc ctaggacatc atgctgtgtc taatggaacc     180
aaagtagaca cccttactga aaaaggaata gaagttgtca atgcaacaga aacagttgaa     240

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caaacaaaca tccctaagat ctgctcaaaa ggaacacaga ctgttgacct tggccaatgt	300
ggattactag ggaccgttat tggctctccc caatgtgacc aatttcttga gttctctgct	360
aatttaatag ttgaagaag ggaaggaat gacatttggt atccaggcaa atttgacaat	420
gaagaaacat tgagaaaaat actcagaaaa tccggaggaa ttaaaaagga gaatatggga	480
ttcacatata ccggagttag aaccaatgga gagactagcg catgtagaag gtcaagatct	540
tccttttatg cagagatgaa atggcttcta tccagcacag acaatgggac atttccacaa	600
atgacaaagt cctacaagaa cactaagaag gtaccagctc tgataatctg gggaaatccac	660
cactcaggat caactactga acagactaga ttatatggaa gtgggaataa attgataaca	720
gtttggagtt ccaataacca acaatctttt gtcccaaatc ctggaccaag accgcaatg	780
aatggtcaat caggaagaat tgactttcac tggctgatgc tagatcccaa tgatactgtc	840
actttcagtt ttaatggggc ctttatagca cctgaccgcg ccagttttct aagaggtaaa	900
tctctaggaa tccaaagtga tgcacaactt gacaataatt gtgaaggtga atgctatcat	960
attggaggta ctataattag caacttgccc tttcaaaa ttaatagtag ggcaatcgga	1020
aatgcccga gatacgtgaa gcagaagac ttaatgctag caacaggaat gaaaaatgtt	1080
cctgaagctc ctgcacataa acaactaact catcacatgc gcaaaaaaag aggtttattt	1140
ggtgcaatag caggattcat tgaatggg tgggaaggat taatagacgg atggtatgga	1200
tataagcatc agaatgcaca aggagaaggg actgctgcag actacaaaag tacacaatct	1260
gctatcaacc aaataaccgg aaaattgaac agactaatag aaaaaaccaa ccagcaattc	1320
gaactaatag ataatgagtt caatgaata gaaaaacaaa ttggcaatgt tattaactgg	1380
actagagatt ctatcatoga agtatggtca tataatgcag agttcctcgt agcagtgagg	1440
aatcaacaca ctattgattt aactgactca gaaatgaaca aactatatga aaaggaaga	1500
agacaactga gagaaaatgc tgaggaagat ggtaatggct gttttgaaat attccaccaa	1560
tgtgacaatg attgcatggc cagcattaga aacaacacat atgaccataa aaaatacaga	1620
aaagaggcaa tacaaaacag aatccagatt gacgcagtaa agttgagcag tggttacaaa	1680
gatataatc tttggtttag cttcggggca tcatgtttct tatttcttgc cattgcaatg	1740
ggtcttgttt tcatatgtat aaaaaatgga aacatgcggt gcactatttg tatataagag	1800
ctc	1803

&lt;210&gt; SEQ ID NO 47

&lt;211&gt; LENGTH: 1773

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Clone

&lt;400&gt; SEQUENCE: 47

cactttgtga gtctacactt tgattccctt caaacacata caaagagaag agactaatta	60
attaattaat catcttgaga gaaaatgga acaatatcac taataactat actactagta	120
gtaacagcaa gcaatgcaga taaaatctgc atcgccacc agtcaacaaa ctccacagaa	180
actgtggaca cgctaacaga aaccaatggt cctgtgacac atgccaaga attgctccac	240
acagagcata atggaatgct gtgtgcaaca agcctgggac atccccat tctagacaca	300
tgcaactatg aaggactagt ctatggcaac ccttcttctg acctgctgtt gggaggaaga	360
gaatggtcct acatcgtoga aagatcatca gctgtaaatg gaacgtgtta ccctgggaat	420
gtagaaaacc tagaggaact caggacactt tttagtccg ctagtcccta ccaagaatc	480

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caaatcttcc cagacacaac ctggaatgtg acttacactg gaacaagcag agcatgttca 540
ggttcattct acaggagtat gagatggctg actcaaaaga gcggttttta cctgttcaa 600
gacgccaat acacaaataa caggggaaag agcattcttt tcgtgtgggg catacatcac 660
ccaccacct ataccgagca aacaaatttg tacataagaa acgacacaac aacaagcgtg 720
acaacagaag atttgaatag gaccttcaaa ccagtgatag ggccaaggcc ccttgtcaat 780
ggtctgcagg gaagaattga ttattattgg tcggtactaa aaccaggcca aacattgcga 840
gtacgatcca atgggaatct aattgtcca tggatggac acgttcttcc aggagggagc 900
catggaagaa tcctgaagac tgatttaaaa ggtggtaatt gtgtagtgca atgtcagact 960
gaaaagggtg gcttaaacag tacattgccca ttccacaata tcagtaaata tgcatttga 1020
acctgcccc aatatgtaag agttaatagt ctcaaaactgg cagtgggtct gaggaacgtg 1080
cctgctagat caagtagagg actatttga gccatagctg gattcataga aggaggttg 1140
ccaggactag tcgctggctg gtatggtttc cagcattcaa atgatcaagg ggttggatg 1200
gctgcagata gggattcaac tcaaaaggca attgataaaa taacatccaa ggtgaataat 1260
atagtcgaca agatgaacaa gcaatatgaa ataattgatc atgaatttag tgaggttga 1320
actagactca atatgatcaa taataagatt gatgacaaa tacaagcgt atgggcatat 1380
aatgcagaat tgctagtact acttgaatc caaaaaacac tcgatgagca tgatgcgaac 1440
gtgaacaatc tatatacaa ggtgaagagg gcaactggct ccaatgctat ggaagatggg 1500
aaaggctggt tcgagctata ccataaatgt gatgatcagt gcatggaac aattcggac 1560
gggacctata ataggagaaa gtatagagag gaatcaagac tagaaaggca gaaaatagag 1620
ggggttaagc tggaatctga gggaaactac aaaatcctca ccatttattc gactgtgcc 1680
tcactcttg tgcttgcgaat ggggttggct gccttctgt tctgggcat gtccaatgga 1740
tcttgcatg gcaacatttg tatataagag etc 1773

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&lt;210&gt; SEQ ID NO 48

&lt;211&gt; LENGTH: 565

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Clone

&lt;400&gt; SEQUENCE: 48

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Met Lys Val Lys Leu Leu Val Leu Leu Cys Thr Phe Thr Ala Thr Tyr
 1             5             10             15
Ala Asp Thr Ile Cys Ile Gly Tyr His Ala Asn Asn Ser Thr Asp Thr
 20             25             30
Val Asp Thr Val Leu Glu Lys Asn Val Thr Val Thr His Ser Val Asn
 35             40             45
Leu Leu Glu Asn Ser His Asn Gly Lys Leu Cys Leu Leu Lys Gly Ile
 50             55             60
Ala Pro Leu Gln Leu Gly Asn Cys Ser Val Ala Gly Trp Ile Leu Gly
 65             70             75             80
Asn Pro Glu Cys Glu Leu Leu Ile Ser Lys Glu Ser Trp Ser Tyr Ile
 85             90             95
Val Glu Lys Pro Asn Pro Glu Asn Gly Thr Cys Tyr Pro Gly His Phe
100             105             110
Ala Asp Tyr Glu Glu Leu Arg Glu Gln Leu Ser Ser Val Ser Ser Phe
115             120             125

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Glu Arg Phe Glu Ile Phe Pro Lys Glu Ser Ser Trp Pro Asn His Thr  
 130 135 140  
 Val Thr Gly Val Ser Ala Ser Cys Ser His Asn Gly Glu Ser Ser Phe  
 145 150 155 160  
 Tyr Arg Asn Leu Leu Trp Leu Thr Gly Lys Asn Gly Leu Tyr Pro Asn  
 165 170 175  
 Leu Ser Lys Ser Tyr Ala Asn Asn Lys Glu Lys Glu Val Leu Val Leu  
 180 185 190  
 Trp Gly Val His His Pro Pro Asn Ile Gly Asp Gln Lys Ala Leu Tyr  
 195 200 205  
 His Thr Glu Asn Ala Tyr Val Ser Val Val Ser Ser His Tyr Ser Arg  
 210 215 220  
 Lys Phe Thr Pro Glu Ile Ala Lys Arg Pro Lys Val Arg Asp Gln Glu  
 225 230 235 240  
 Gly Arg Ile Asn Tyr Tyr Trp Thr Leu Leu Glu Pro Gly Asp Thr Ile  
 245 250 255  
 Ile Phe Glu Ala Asn Gly Asn Leu Ile Ala Pro Arg Tyr Ala Phe Ala  
 260 265 270  
 Leu Ser Arg Gly Phe Gly Ser Gly Ile Ile Asn Ser Asn Ala Pro Met  
 275 280 285  
 Asp Lys Cys Asp Ala Lys Cys Gln Thr Pro Gln Gly Ala Ile Asn Ser  
 290 295 300  
 Ser Leu Pro Phe Gln Asn Val His Pro Val Thr Ile Gly Glu Cys Pro  
 305 310 315 320  
 Lys Tyr Val Arg Ser Ala Lys Leu Arg Met Val Thr Gly Leu Arg Asn  
 325 330 335  
 Ile Pro Ser Ile Gln Ser Arg Gly Leu Phe Gly Ala Ile Ala Gly Phe  
 340 345 350  
 Ile Glu Gly Gly Trp Thr Gly Met Val Asp Gly Trp Tyr Gly Tyr His  
 355 360 365  
 His Gln Asn Glu Gln Gly Ser Gly Tyr Ala Ala Asp Gln Lys Ser Thr  
 370 375 380  
 Gln Asn Ala Ile Asn Gly Ile Thr Asn Lys Val Asn Ser Val Ile Glu  
 385 390 395 400  
 Lys Met Asn Thr Gln Phe Thr Ala Val Gly Lys Glu Phe Asn Lys Leu  
 405 410 415  
 Glu Arg Arg Met Glu Asn Leu Asn Lys Lys Val Asp Asp Gly Phe Ile  
 420 425 430  
 Asp Ile Trp Thr Tyr Asn Ala Glu Leu Leu Val Leu Leu Glu Asn Glu  
 435 440 445  
 Arg Thr Leu Asp Phe His Asp Ser Asn Val Lys Asn Leu Tyr Glu Lys  
 450 455 460  
 Val Lys Ser Gln Leu Lys Asn Asn Ala Lys Glu Ile Gly Asn Gly Cys  
 465 470 475 480  
 Phe Glu Phe Tyr His Lys Cys Asn Asp Glu Cys Met Glu Ser Val Lys  
 485 490 495  
 Asn Gly Thr Tyr Asp Tyr Pro Lys Tyr Ser Glu Glu Ser Lys Leu Asn  
 500 505 510  
 Arg Glu Lys Ile Asp Gly Val Lys Leu Glu Ser Met Gly Val Tyr Gln  
 515 520 525  
 Ile Leu Ala Ile Tyr Ser Thr Val Ala Ser Ser Leu Val Leu Leu Val  
 530 535 540  
 Ser Leu Gly Ala Ile Ser Phe Trp Met Cys Ser Asn Gly Ser Leu Gln

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545                550                555                560
Cys Arg Ile Cys Ile
                    565

<210> SEQ ID NO 49
<211> LENGTH: 565
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Clone

<400> SEQUENCE: 49
Met Lys Val Lys Leu Leu Val Leu Leu Cys Thr Phe Thr Ala Thr Tyr
1                               5                               10                               15
Ala Asp Thr Ile Cys Ile Gly Tyr His Ala Asn Asn Ser Thr Asp Thr
                20                               25                               30
Val Asp Thr Val Leu Glu Lys Asn Val Thr Val Thr His Ser Val Asn
                35                               40                               45
Leu Leu Glu Asp Ser His Asn Gly Lys Leu Cys Leu Leu Lys Gly Ile
50                               55                               60
Ala Pro Leu Gln Leu Gly Asn Cys Ser Val Ala Gly Trp Ile Leu Gly
65                               70                               75                               80
Asn Pro Glu Cys Glu Leu Leu Ile Ser Arg Glu Ser Trp Ser Tyr Ile
                85                               90                               95
Val Glu Lys Pro Asn Pro Glu Asn Gly Thr Cys Tyr Pro Gly His Phe
                100                              105                              110
Ala Asp Tyr Glu Glu Leu Arg Glu Gln Leu Ser Ser Val Ser Ser Phe
                115                              120                              125
Glu Arg Phe Glu Ile Phe Pro Lys Glu Ser Ser Trp Pro Asn His Thr
130                              135                              140
Thr Thr Gly Val Ser Ala Ser Cys Ser His Asn Gly Glu Ser Ser Phe
145                              150                              155                              160
Tyr Lys Asn Leu Leu Trp Leu Thr Gly Lys Asn Gly Leu Tyr Pro Asn
                165                              170                              175
Leu Ser Lys Ser Tyr Ala Asn Asn Lys Glu Lys Glu Val Leu Val Leu
                180                              185                              190
Trp Gly Val His His Pro Pro Asn Ile Gly Asp Gln Arg Ala Leu Tyr
                195                              200                              205
His Lys Glu Asn Ala Tyr Val Ser Val Val Ser Ser His Tyr Ser Arg
210                              215                              220
Lys Phe Thr Pro Glu Ile Ala Lys Arg Pro Lys Val Arg Asp Gln Glu
225                              230                              235                              240
Gly Arg Ile Asn Tyr Tyr Trp Thr Leu Leu Glu Pro Gly Asp Thr Ile
                245                              250                              255
Ile Phe Glu Ala Asn Gly Asn Leu Ile Ala Pro Arg Tyr Ala Phe Ala
                260                              265                              270
Leu Ser Arg Gly Phe Gly Ser Gly Ile Ile Asn Ser Asn Ala Pro Met
275                              280                              285
Asp Glu Cys Asp Ala Lys Cys Gln Thr Pro Gln Gly Ala Ile Asn Ser
290                              295                              300
Ser Leu Pro Phe Gln Asn Val His Pro Val Thr Ile Gly Glu Cys Pro
305                              310                              315                              320
Lys Tyr Val Arg Ser Ala Lys Leu Arg Met Val Thr Gly Leu Arg Asn
                325                              330                              335
Ile Pro Ser Ile Gln Ser Arg Gly Leu Phe Gly Ala Ile Ala Gly Phe
    
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Ile	Glu	Gly	Gly	Trp	Thr	Gly	Met	Val	Asp	Gly	Trp	Tyr	Gly	Tyr	His
	355						360						365		
His	Gln	Asn	Glu	Gln	Gly	Ser	Gly	Tyr	Ala	Ala	Asp	Gln	Lys	Ser	Thr
	370					375					380				
Gln	Asn	Ala	Ile	Asn	Gly	Ile	Thr	Asn	Lys	Val	Asn	Ser	Val	Ile	Glu
	385				390					395					400
Lys	Met	Asn	Thr	Gln	Phe	Thr	Ala	Val	Gly	Lys	Glu	Phe	Asn	Lys	Leu
				405					410					415	
Glu	Arg	Arg	Met	Glu	Asn	Leu	Asn	Lys	Lys	Val	Asp	Asp	Gly	Phe	Ile
			420					425					430		
Asp	Ile	Trp	Thr	Tyr	Asn	Ala	Glu	Leu	Leu	Val	Leu	Leu	Glu	Asn	Glu
		435					440						445		
Arg	Thr	Leu	Asp	Phe	His	Asp	Ser	Asn	Val	Lys	Asn	Leu	Tyr	Glu	Lys
	450					455						460			
Val	Lys	Ser	Gln	Leu	Lys	Asn	Asn	Ala	Lys	Glu	Ile	Gly	Asn	Gly	Cys
	465				470					475					480
Phe	Glu	Phe	Tyr	His	Lys	Cys	Asn	Asp	Glu	Cys	Met	Glu	Ser	Val	Lys
				485					490						495
Asn	Gly	Thr	Tyr	Asp	Tyr	Pro	Lys	Tyr	Ser	Glu	Glu	Ser	Lys	Leu	Asn
			500					505						510	
Arg	Glu	Lys	Ile	Asp	Gly	Val	Lys	Leu	Glu	Ser	Met	Gly	Val	Tyr	Gln
		515					520						525		
Ile	Leu	Ala	Ile	Tyr	Ser	Thr	Val	Ala	Ser	Ser	Leu	Val	Leu	Leu	Val
	530					535					540				
Ser	Leu	Gly	Ala	Ile	Ser	Phe	Trp	Met	Cys	Ser	Asn	Gly	Ser	Leu	Gln
	545				550					555					560
Cys	Arg	Ile	Cys	Ile											
				565											

&lt;210&gt; SEQ ID NO 50

&lt;211&gt; LENGTH: 566

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Clone

&lt;400&gt; SEQUENCE: 50

Met	Lys	Thr	Ile	Ile	Ala	Leu	Ser	Tyr	Ile	Leu	Cys	Leu	Val	Phe	Thr
1				5					10					15	
Gln	Lys	Leu	Pro	Gly	Asn	Asp	Asn	Ser	Thr	Ala	Thr	Leu	Cys	Leu	Gly
			20					25					30		
His	His	Ala	Val	Pro	Asn	Gly	Thr	Ile	Val	Lys	Thr	Ile	Thr	Asn	Asp
		35					40					45			
Gln	Ile	Glu	Val	Thr	Asn	Ala	Thr	Glu	Leu	Val	Gln	Ser	Ser	Ser	Thr
	50					55					60				
Gly	Glu	Ile	Cys	Asp	Ser	Pro	His	Gln	Ile	Leu	Asp	Gly	Glu	Asn	Cys
	65				70					75				80	
Thr	Leu	Ile	Asp	Ala	Leu	Leu	Gly	Asp	Pro	Gln	Cys	Asp	Gly	Phe	Gln
				85					90					95	
Asn	Lys	Lys	Trp	Asp	Leu	Phe	Val	Glu	Arg	Ser	Lys	Ala	Tyr	Ser	Asn
			100					105					110		
Cys	Tyr	Pro	Tyr	Asp	Val	Pro	Asp	Tyr	Ala	Ser	Leu	Arg	Ser	Leu	Val
		115					120					125			
Ala	Ser	Ser	Gly	Thr	Leu	Glu	Phe	Asn	Asn	Glu	Ser	Phe	Asn	Trp	Thr

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130						135										140
Gly	Val	Thr	Gln	Asn	Gly	Thr	Ser	Ser	Ala	Cys	Ile	Arg	Arg	Ser	Asn	
145					150					155					160	
Asn	Ser	Phe	Phe	Ser	Arg	Leu	Asn	Trp	Leu	Thr	His	Leu	Lys	Phe	Lys	
				165					170					175		
Tyr	Pro	Ala	Leu	Asn	Val	Thr	Met	Pro	Asn	Asn	Glu	Lys	Phe	Asp	Lys	
			180					185					190			
Leu	Tyr	Ile	Trp	Gly	Val	His	His	Pro	Gly	Thr	Asp	Asn	Asp	Gln	Ile	
		195					200					205				
Phe	Leu	Tyr	Ala	Gln	Ala	Ser	Gly	Arg	Ile	Thr	Val	Ser	Thr	Lys	Arg	
210						215					220					
Ser	Gln	Gln	Thr	Val	Ile	Pro	Asn	Ile	Gly	Ser	Arg	Pro	Arg	Val	Arg	
225					230					235					240	
Asn	Ile	Pro	Ser	Arg	Ile	Ser	Ile	Tyr	Trp	Thr	Ile	Val	Lys	Pro	Gly	
				245					250					255		
Asp	Ile	Leu	Leu	Ile	Asn	Ser	Thr	Gly	Asn	Leu	Ile	Ala	Pro	Arg	Gly	
		260						265					270			
Tyr	Phe	Lys	Ile	Arg	Ser	Gly	Lys	Ser	Ser	Ile	Met	Arg	Ser	Asp	Ala	
		275					280					285				
Pro	Ile	Gly	Lys	Cys	Asn	Ser	Glu	Cys	Ile	Thr	Pro	Asn	Gly	Ser	Ile	
290					295						300					
Pro	Asn	Asp	Lys	Pro	Phe	Gln	Asn	Val	Asn	Arg	Ile	Thr	Tyr	Gly	Ala	
305					310					315					320	
Cys	Pro	Arg	Tyr	Val	Lys	Gln	Asn	Thr	Leu	Lys	Leu	Ala	Thr	Gly	Met	
				325					330					335		
Arg	Asn	Val	Pro	Glu	Lys	Gln	Thr	Arg	Gly	Ile	Phe	Gly	Ala	Ile	Ala	
		340						345					350			
Gly	Phe	Ile	Glu	Asn	Gly	Trp	Glu	Gly	Met	Val	Asp	Gly	Trp	Tyr	Gly	
		355					360					365				
Phe	Arg	His	Gln	Asn	Ser	Glu	Gly	Ile	Gly	Gln	Ala	Ala	Asp	Leu	Lys	
370					375						380					
Ser	Thr	Gln	Ala	Ala	Ile	Asp	Gln	Ile	Asn	Gly	Lys	Leu	Asn	Arg	Leu	
385					390					395					400	
Ile	Gly	Lys	Thr	Asn	Glu	Lys	Phe	His	Gln	Ile	Glu	Lys	Glu	Phe	Ser	
				405					410					415		
Glu	Val	Glu	Gly	Arg	Ile	Gln	Asp	Leu	Glu	Lys	Tyr	Val	Glu	Asp	Thr	
			420					425					430			
Lys	Ile	Asp	Leu	Trp	Ser	Tyr	Asn	Ala	Glu	Leu	Leu	Val	Ala	Leu	Glu	
		435					440						445			
Asn	Gln	His	Thr	Ile	Asp	Leu	Thr	Asp	Ser	Glu	Met	Asn	Lys	Leu	Phe	
450					455						460					
Glu	Lys	Thr	Lys	Lys	Gln	Leu	Arg	Glu	Asn	Ala	Glu	Asp	Met	Gly	Asn	
465					470					475					480	
Gly	Cys	Phe	Lys	Ile	Tyr	His	Lys	Cys	Asp	Asn	Ala	Cys	Ile	Gly	Ser	
				485					490					495		
Ile	Arg	Asn	Gly	Thr	Tyr	Asp	His	Asp	Val	Tyr	Arg	Asp	Glu	Ala	Leu	
			500					505					510			
Asn	Asn	Arg	Phe	Gln	Ile	Lys	Gly	Val	Glu	Leu	Lys	Ser	Gly	Tyr	Lys	
		515					520						525			
Asp	Trp	Ile	Leu	Trp	Ile	Ser	Phe	Ala	Ile	Ser	Cys	Phe	Leu	Leu	Cys	
530						535					540					
Val	Ala	Leu	Leu	Gly	Phe	Ile	Met	Trp	Ala	Cys	Gln	Lys	Gly	Asn	Ile	
545				550						555					560	

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Arg Cys Asn Ile Cys Ile  
565

<210> SEQ ID NO 51  
<211> LENGTH: 566  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Clone

<400> SEQUENCE: 51

Met Lys Thr Ile Ile Ala Leu Ser Tyr Ile Leu Cys Leu Val Phe Thr  
1 5 10 15  
Gln Lys Leu Pro Gly Asn Asp Asn Ser Thr Ala Thr Leu Cys Leu Gly  
20 25 30  
His His Ala Val Pro Asn Gly Thr Ile Val Lys Thr Ile Thr Asn Asp  
35 40 45  
Gln Ile Glu Val Thr Asn Ala Thr Glu Leu Val Gln Ser Ser Ser Thr  
50 55 60  
Gly Gly Ile Cys Asp Ser Pro His Gln Ile Leu Asp Gly Glu Asn Cys  
65 70 75 80  
Thr Leu Ile Asp Ala Leu Leu Gly Asp Pro Gln Cys Asp Gly Phe Gln  
85 90 95  
Asn Lys Lys Trp Asp Leu Phe Val Glu Arg Ser Lys Ala Tyr Ser Asn  
100 105 110  
Cys Tyr Pro Tyr Asp Val Pro Asp Tyr Ala Ser Leu Arg Ser Leu Val  
115 120 125  
Ala Ser Ser Gly Thr Leu Glu Phe Asn Asp Glu Ser Phe Asn Trp Thr  
130 135 140  
Gly Val Thr Gln Asn Gly Thr Ser Ser Ala Cys Lys Arg Arg Ser Asn  
145 150 155 160  
Asn Ser Phe Phe Ser Arg Leu Asn Trp Leu Thr His Leu Lys Phe Lys  
165 170 175  
Tyr Pro Ala Leu Asn Val Thr Met Pro Asn Asn Glu Lys Phe Asp Lys  
180 185 190  
Leu Tyr Ile Trp Gly Val His His Pro Gly Thr Asp Asn Asp Gln Ile  
195 200 205  
Phe Leu His Ala Gln Ala Ser Gly Arg Ile Thr Val Ser Thr Lys Arg  
210 215 220  
Ser Gln Gln Thr Val Ile Pro Asn Ile Gly Ser Arg Pro Arg Ile Arg  
225 230 235 240  
Asn Ile Pro Ser Arg Ile Ser Ile Tyr Trp Thr Ile Val Lys Pro Gly  
245 250 255  
Asp Ile Leu Leu Ile Asn Ser Thr Gly Asn Leu Ile Ala Pro Arg Gly  
260 265 270  
Tyr Phe Lys Ile Arg Ser Gly Lys Ser Ser Ile Met Arg Ser Asp Ala  
275 280 285  
Pro Ile Gly Lys Cys Asn Ser Glu Cys Ile Thr Pro Asn Gly Ser Ile  
290 295 300  
Pro Asn Asp Lys Pro Phe Gln Asn Val Asn Arg Ile Thr Tyr Gly Ala  
305 310 315 320  
Cys Pro Arg Tyr Val Lys Gln Asn Thr Leu Lys Leu Ala Thr Gly Met  
325 330 335  
Arg Asn Val Pro Glu Lys Gln Thr Arg Gly Ile Phe Gly Ala Ile Ala  
340 345 350

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Gly Phe Ile Glu Asn Gly Trp Glu Gly Met Val Asp Gly Trp Tyr Gly  
           355  360  365  
 Phe Arg His Gln Asn Ser Glu Gly Ile Gly Gln Ala Ala Asp Leu Lys  
           370  375  380  
 Ser Thr Gln Ala Ala Ile Asn Gln Ile Asn Gly Lys Leu Asn Arg Leu  
           385  390  395  400  
 Ile Gly Lys Thr Asn Glu Lys Phe His Gln Ile Glu Lys Glu Phe Ser  
   405  410  415  
 Glu Val Glu Gly Arg Ile Gln Asp Leu Glu Lys Tyr Val Glu Asp Thr  
   420  425  430  
 Lys Ile Asp Leu Trp Ser Tyr Asn Ala Glu Leu Leu Val Ala Leu Glu  
   435  440  445  
 Asn Gln His Thr Ile Asp Leu Thr Asp Ser Glu Met Asn Lys Leu Phe  
   450  455  460  
 Glu Arg Thr Lys Lys Gln Leu Arg Glu Asn Ala Glu Asp Met Gly Asn  
   465  470  475  480  
 Gly Cys Phe Lys Ile Tyr His Lys Cys Asp Asn Ala Cys Ile Gly Ser  
   485  490  495  
 Ile Arg Asn Gly Thr Tyr Asp His Asp Val Tyr Arg Asp Glu Ala Leu  
   500  505  510  
 Asn Asn Arg Phe Gln Ile Lys Gly Val Glu Leu Lys Ser Gly Tyr Lys  
   515  520  525  
 Asp Trp Ile Leu Trp Ile Ser Phe Ala Ile Ser Cys Phe Leu Leu Cys  
   530  535  540  
 Val Ala Leu Leu Gly Phe Ile Met Trp Ala Cys Gln Lys Gly Asn Ile  
   545  550  555  560  
 Arg Cys Asn Ile Cys Ile  
   565

<210> SEQ ID NO 52  
 <211> LENGTH: 585  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Clone

<400> SEQUENCE: 52

Met Lys Ala Ile Ile Val Leu Leu Met Val Val Thr Ser Asn Ala Asp  
 1                  5  10  15  
 Arg Ile Cys Thr Gly Ile Thr Ser Ser Asn Ser Pro His Val Val Lys  
           20  25  30  
 Thr Ala Thr Gln Gly Glu Val Asn Val Thr Gly Val Ile Pro Leu Thr  
           35  40  45  
 Thr Thr Pro Thr Lys Ser His Phe Ala Asn Leu Lys Gly Thr Glu Thr  
           50  55  60  
 Arg Gly Lys Leu Cys Pro Lys Cys Leu Asn Cys Thr Asp Leu Asp Val  
           65  70  75  80  
 Ala Leu Gly Arg Pro Lys Cys Thr Gly Asn Ile Pro Ser Ala Arg Val  
   85  90  95  
 Ser Ile Leu His Glu Val Arg Pro Val Thr Ser Gly Cys Phe Pro Ile  
   100  105  110  
 Met His Asp Arg Thr Lys Ile Arg Gln Leu Pro Lys Leu Leu Arg Gly  
   115  120  125  
 Tyr Glu His Ile Arg Leu Ser Thr His Asn Val Ile Asn Ala Glu Asn  
           130  135  140

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Ala Pro Gly Gly Pro Tyr Lys Ile Gly Thr Ser Gly Ser Cys Pro Asn  
 145 150 155 160  
 Val Thr Asn Gly Asn Gly Phe Phe Ala Thr Met Ala Trp Ala Val Pro  
 165 170 175  
 Lys Asn Asp Asn Asn Lys Thr Ala Thr Asn Ser Leu Thr Ile Glu Val  
 180 185 190  
 Pro Tyr Ile Cys Thr Glu Gly Glu Asp Gln Ile Thr Val Trp Gly Phe  
 195 200 205  
 His Ser Asp Asn Glu Thr Gln Met Ala Lys Leu Tyr Gly Asp Ser Lys  
 210 215 220  
 Pro Gln Lys Phe Thr Ser Ser Ala Asn Gly Val Thr Thr His Tyr Val  
 225 230 235 240  
 Ser Gln Ile Gly Gly Phe Pro Asn Gln Thr Glu Asp Gly Gly Leu Pro  
 245 250 255  
 Gln Ser Gly Arg Ile Val Val Asp Tyr Met Val Gln Lys Ser Gly Lys  
 260 265 270  
 Thr Gly Thr Ile Thr Tyr Gln Arg Gly Ile Leu Leu Pro Gln Lys Val  
 275 280 285  
 Trp Cys Ala Ser Gly Arg Ser Lys Val Ile Lys Gly Ser Leu Pro Leu  
 290 295 300  
 Ile Gly Glu Ala Asp Cys Leu His Glu Lys Tyr Gly Gly Leu Asn Lys  
 305 310 315 320  
 Ser Lys Pro Tyr Tyr Thr Gly Glu His Ala Lys Ala Ile Gly Asn Cys  
 325 330 335  
 Pro Ile Trp Val Lys Thr Pro Leu Lys Leu Ala Asn Gly Thr Lys Tyr  
 340 345 350  
 Arg Pro Pro Ala Lys Leu Leu Lys Glu Arg Gly Phe Phe Gly Ala Ile  
 355 360 365  
 Ala Gly Phe Leu Glu Gly Gly Trp Glu Gly Met Ile Ala Gly Trp His  
 370 375 380  
 Gly Tyr Thr Ser His Gly Ala His Gly Val Ala Val Ala Ala Asp Leu  
 385 390 395 400  
 Lys Ser Thr Gln Glu Ala Ile Asn Lys Ile Thr Lys Asn Leu Asn Ser  
 405 410 415  
 Leu Ser Glu Leu Glu Val Lys Asn Leu Gln Arg Leu Ser Gly Ala Met  
 420 425 430  
 Asp Glu Leu His Asn Glu Ile Leu Glu Leu Asp Glu Lys Val Asp Asp  
 435 440 445  
 Leu Arg Ala Asp Thr Ile Ser Ser Gln Ile Glu Leu Ala Val Leu Leu  
 450 455 460  
 Ser Asn Glu Gly Ile Ile Asn Ser Glu Asp Glu His Leu Leu Ala Leu  
 465 470 475 480  
 Glu Arg Lys Leu Lys Lys Met Leu Gly Pro Ser Ala Val Glu Ile Gly  
 485 490 495  
 Asn Gly Cys Phe Glu Thr Lys His Lys Cys Asn Gln Thr Cys Leu Asp  
 500 505 510  
 Arg Ile Ala Ala Gly Thr Phe Asp Ala Gly Glu Phe Ser Leu Pro Thr  
 515 520 525  
 Phe Asp Ser Leu Asn Ile Thr Ala Ala Ser Leu Asn Asp Asp Gly Leu  
 530 535 540  
 Asp Asn His Thr Ile Leu Leu Tyr Tyr Ser Thr Ala Ala Ser Ser Leu  
 545 550 555 560

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Ala Val Thr Leu Met Ile Ala Ile Phe Val Val Tyr Met Val Ser Arg  
565 570 575

Asp Asn Val Ser Cys Ser Ile Cys Leu  
580 585

<210> SEQ ID NO 53  
 <211> LENGTH: 584  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Clone

<400> SEQUENCE: 53

Met Lys Ala Ile Ile Val Leu Leu Met Val Val Thr Ser Asn Ala Asp  
1 5 10 15

Arg Ile Cys Thr Gly Ile Thr Ser Ser Asn Ser Pro His Val Val Lys  
20 25 30

Thr Ala Thr Gln Gly Glu Val Asn Val Thr Gly Val Ile Pro Leu Thr  
35 40 45

Thr Thr Pro Thr Lys Ser Tyr Phe Ala Asn Leu Lys Gly Thr Arg Thr  
50 55 60

Arg Gly Lys Leu Cys Pro Asp Cys Leu Asn Cys Thr Asp Leu Asp Val  
65 70 75 80

Ala Leu Gly Arg Pro Met Cys Val Gly Thr Thr Pro Ser Ala Lys Ala  
85 90 95

Ser Ile Leu His Glu Val Lys Pro Val Thr Ser Gly Cys Phe Pro Ile  
100 105 110

Met His Asp Arg Thr Lys Ile Arg Gln Leu Pro Asn Leu Leu Arg Gly  
115 120 125

Tyr Glu Asn Ile Arg Leu Ser Thr Gln Asn Val Ile Asp Ala Glu Lys  
130 135 140

Ala Pro Gly Gly Pro Tyr Arg Leu Gly Thr Ser Gly Ser Cys Pro Asn  
145 150 155 160

Ala Thr Ser Lys Ser Gly Phe Phe Ala Thr Met Ala Trp Ala Val Pro  
165 170 175

Lys Asp Asn Asn Lys Asn Ala Thr Asn Pro Leu Thr Val Glu Val Pro  
180 185 190

Tyr Ile Cys Thr Glu Gly Glu Asp Gln Ile Thr Val Trp Gly Phe His  
195 200 205

Ser Asp Asn Lys Thr Gln Met Lys Asn Leu Tyr Gly Asp Ser Asn Pro  
210 215 220

Gln Lys Phe Thr Ser Ser Ala Asn Gly Val Thr Thr His Tyr Val Ser  
225 230 235 240

Gln Ile Gly Ser Phe Pro Asp Gln Thr Glu Asp Gly Gly Leu Pro Gln  
245 250 255

Ser Gly Arg Ile Val Val Asp Tyr Met Met Gln Lys Pro Gly Lys Thr  
260 265 270

Gly Thr Ile Val Tyr Gln Arg Gly Val Leu Leu Pro Gln Lys Val Trp  
275 280 285

Cys Ala Ser Gly Arg Ser Lys Val Ile Lys Gly Ser Leu Pro Leu Ile  
290 295 300

Gly Glu Ala Asp Cys Leu His Glu Lys Tyr Gly Gly Leu Asn Lys Ser  
305 310 315 320

Lys Pro Tyr Tyr Thr Gly Glu His Ala Lys Ala Ile Gly Asn Cys Pro  
325 330 335

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Ile Trp Val Lys Thr Pro Leu Lys Leu Ala Asn Gly Thr Lys Tyr Arg
      340                      345                      350

Pro Pro Ala Lys Leu Leu Lys Glu Arg Gly Phe Phe Gly Ala Ile Ala
      355                      360                      365

Gly Phe Leu Glu Gly Gly Trp Glu Gly Met Ile Ala Gly Trp His Gly
      370                      375                      380

Tyr Thr Ser His Gly Ala His Gly Val Ala Val Ala Ala Asp Leu Lys
      385                      390                      395                      400

Ser Thr Gln Glu Ala Ile Asn Lys Ile Thr Lys Asn Leu Asn Ser Leu
      405                      410                      415

Ser Glu Leu Glu Val Lys Asn Leu Gln Arg Leu Ser Gly Ala Met Asp
      420                      425                      430

Glu Leu His Asn Glu Ile Leu Glu Leu Asp Glu Lys Val Asp Asp Leu
      435                      440                      445

Arg Ala Asp Thr Ile Ser Ser Gln Ile Glu Leu Ala Val Leu Leu Ser
      450                      455                      460

Asn Glu Gly Ile Ile Asn Ser Glu Asp Glu His Leu Leu Ala Leu Glu
      465                      470                      475                      480

Arg Lys Leu Lys Lys Met Leu Gly Pro Ser Ala Val Glu Ile Gly Asn
      485                      490                      495

Gly Cys Phe Glu Thr Lys His Lys Cys Asn Gln Thr Cys Leu Asp Arg
      500                      505                      510

Ile Ala Ala Gly Thr Phe Asn Ala Gly Glu Phe Ser Leu Pro Thr Phe
      515                      520                      525

Asp Ser Leu Asn Ile Thr Ala Ala Ser Leu Asn Asp Asp Gly Leu Asp
      530                      535                      540

Asn His Thr Ile Leu Leu Tyr Tyr Ser Thr Ala Ala Ser Ser Leu Ala
      545                      550                      555                      560

Val Thr Leu Met Leu Ala Ile Phe Ile Val Tyr Met Val Ser Arg Asp
      565                      570                      575

Asn Val Ser Cys Ser Ile Cys Leu
      580

<210> SEQ ID NO 54
<211> LENGTH: 562
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Clone

<400> SEQUENCE: 54

Met Ala Ile Ile Tyr Leu Ile Leu Leu Phe Thr Ala Val Arg Gly Asp
 1          5          10          15

Gln Ile Cys Ile Gly Tyr His Ala Asn Asn Ser Thr Glu Lys Val Asp
 20          25          30

Thr Ile Leu Glu Arg Asn Val Thr Val Thr His Ala Lys Asp Ile Leu
 35          40          45

Glu Lys Thr His Asn Gly Lys Leu Cys Lys Leu Asn Gly Ile Pro Pro
 50          55          60

Leu Glu Leu Gly Asp Cys Ser Ile Ala Gly Trp Leu Leu Gly Asn Pro
 65          70          75          80

Glu Cys Asp Arg Leu Leu Ser Val Pro Glu Trp Ser Tyr Ile Met Glu
 85          90          95

Lys Glu Asn Pro Arg Asp Gly Leu Cys Tyr Pro Gly Ser Phe Asn Asp
100         105         110

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Tyr Glu Glu Leu Lys His Leu Leu Ser Ser Val Lys His Phe Glu Lys  
 115 120 125  
 Val Lys Ile Leu Pro Lys Asp Arg Trp Thr Gln His Thr Thr Thr Gly  
 130 135 140  
 Gly Ser Arg Ala Cys Ala Val Ser Gly Asn Pro Ser Phe Phe Arg Asn  
 145 150 155 160  
 Met Val Trp Leu Thr Lys Lys Glu Ser Asn Tyr Pro Val Ala Lys Gly  
 165 170 175  
 Ser Tyr Asn Asn Thr Ser Gly Glu Gln Met Leu Ile Ile Trp Gly Val  
 180 185 190  
 His His Pro Asn Asp Glu Thr Glu Gln Arg Thr Leu Tyr Gln Asn Val  
 195 200 205  
 Gly Thr Tyr Val Ser Val Gly Thr Ser Thr Leu Asn Lys Arg Ser Thr  
 210 215 220  
 Pro Asp Ile Ala Thr Arg Pro Lys Val Asn Gly Leu Gly Ser Arg Met  
 225 230 235 240  
 Glu Phe Ser Trp Thr Leu Leu Asp Met Trp Asp Thr Ile Asn Phe Glu  
 245 250 255  
 Ser Thr Gly Asn Leu Ile Ala Pro Glu Tyr Gly Phe Lys Ile Ser Lys  
 260 265 270  
 Arg Gly Ser Ser Gly Ile Met Lys Thr Glu Gly Thr Leu Glu Asn Cys  
 275 280 285  
 Glu Thr Lys Cys Gln Thr Pro Leu Gly Ala Ile Asn Thr Thr Leu Pro  
 290 295 300  
 Phe His Asn Val His Pro Leu Thr Ile Gly Glu Cys Pro Lys Tyr Val  
 305 310 315  
 Lys Ser Glu Lys Leu Val Leu Ala Thr Gly Leu Arg Asn Val Pro Gln  
 325 330 335  
 Ile Glu Ser Arg Gly Leu Phe Gly Ala Ile Ala Gly Phe Ile Glu Gly  
 340 345 350  
 Gly Trp Gln Gly Met Val Asp Gly Trp Tyr Gly Tyr His His Ser Asn  
 355 360 365  
 Asp Gln Gly Ser Gly Tyr Ala Ala Asp Lys Glu Ser Thr Gln Lys Ala  
 370 375 380  
 Phe Asp Gly Ile Thr Asn Lys Val Asn Ser Val Ile Glu Lys Met Asn  
 385 390 395 400  
 Thr Gln Phe Glu Ala Val Gly Lys Glu Phe Ser Asn Leu Glu Arg Arg  
 405 410 415  
 Leu Glu Asn Leu Asn Lys Lys Met Glu Asp Gly Phe Leu Asp Val Trp  
 420 425 430  
 Thr Tyr Asn Ala Glu Leu Leu Val Leu Met Glu Asn Glu Arg Thr Leu  
 435 440 445  
 Asp Phe His Asp Ser Asn Val Lys Asn Leu Tyr Asp Lys Val Arg Met  
 450 455 460  
 Gln Leu Arg Asp Asn Val Lys Glu Leu Gly Asn Gly Cys Phe Glu Phe  
 465 470 475 480  
 Tyr His Lys Cys Asp Asp Glu Cys Met Asn Ser Val Lys Asn Gly Thr  
 485 490 495  
 Tyr Asp Tyr Pro Lys Tyr Glu Glu Glu Ser Lys Leu Asn Arg Asn Glu  
 500 505 510  
 Ile Lys Gly Val Lys Leu Ser Ser Met Gly Val Tyr Gln Ile Leu Ala  
 515 520 525  
 Ile Tyr Ala Thr Val Ala Gly Ser Leu Ser Leu Ala Ile Met Met Ala

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530	535	540
Gly Ile Ser Phe Trp Met Cys Ser Asn Gly Ser Leu Gln Cys Arg Ile		
545	550	555 560
Cys Ile		
<210> SEQ ID NO 55		
<211> LENGTH: 567		
<212> TYPE: PRT		
<213> ORGANISM: Artificial Sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: Clone		
<400> SEQUENCE: 55		
Met Glu Lys Ile Val Leu Leu Leu Ala Ile Val Ser Leu Val Lys Ser		
1	5	10 15
Asp Gln Ile Cys Ile Gly Tyr His Ala Asn Asn Ser Thr Glu Gln Val		
	20	25 30
Asp Thr Ile Met Glu Lys Asn Val Thr Val Thr His Ala Gln Asp Ile		
	35	40 45
Leu Glu Lys Thr His Asn Gly Lys Leu Cys Asp Leu Asp Gly Val Lys		
	50	55 60
Pro Leu Ile Leu Arg Asp Cys Ser Val Ala Gly Trp Leu Leu Gly Asn		
	65	70 75 80
Pro Met Cys Asp Glu Phe Ile Asn Val Pro Glu Trp Ser Tyr Ile Val		
	85	90 95
Glu Lys Ala Asn Pro Ala Asn Asp Leu Cys Tyr Pro Gly Asn Phe Asn		
	100	105 110
Asp Tyr Glu Glu Leu Lys His Leu Leu Ser Arg Ile Asn His Phe Glu		
	115	120 125
Lys Ile Gln Ile Ile Pro Lys Ser Ser Trp Ser Asp His Glu Ala Ser		
	130	135 140
Ser Gly Val Ser Ser Ala Cys Pro Tyr Gln Gly Thr Pro Ser Phe Phe		
	145	150 155 160
Arg Asn Val Val Trp Leu Ile Lys Lys Asn Asn Thr Tyr Pro Thr Ile		
	165	170 175
Lys Arg Ser Tyr Asn Asn Thr Asn Gln Glu Asp Leu Leu Ile Leu Trp		
	180	185 190
Gly Ile His His Ser Asn Asp Ala Ala Glu Gln Thr Lys Leu Tyr Gln		
	195	200 205
Asn Pro Thr Thr Tyr Ile Ser Val Gly Thr Ser Thr Leu Asn Gln Arg		
	210	215 220
Leu Val Pro Lys Ile Ala Thr Arg Ser Lys Val Asn Gly Gln Ser Gly		
	225	230 235 240
Arg Met Asp Phe Phe Trp Thr Ile Leu Lys Pro Asn Asp Ala Ile Asn		
	245	250 255
Phe Glu Ser Asn Gly Asn Phe Ile Ala Pro Glu Tyr Ala Tyr Lys Ile		
	260	265 270
Val Lys Lys Gly Asp Ser Ala Ile Val Lys Ser Glu Val Glu Tyr Gly		
	275	280 285
Asn Cys Asn Thr Lys Cys Gln Thr Pro Ile Gly Ala Ile Asn Ser Ser		
	290	295 300
Met Pro Phe His Asn Ile His Pro Leu Thr Ile Gly Glu Cys Pro Lys		
	305	310 315 320
Tyr Val Lys Ser Asn Lys Leu Val Leu Ala Thr Gly Leu Arg Asn Ser		
	325	330 335

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Pro Leu Arg Glu Arg Arg Arg Lys Arg Gly Leu Phe Gly Ala Ile Ala  
                   340                                  345                                  350  
 Gly Phe Ile Glu Gly Gly Trp Gln Gly Met Val Asp Gly Trp Tyr Gly  
                   355                                  360                                  365  
 Tyr His His Ser Asn Glu Gln Gly Ser Gly Tyr Ala Ala Asp Lys Glu  
                   370                                  375                                  380  
 Ser Thr Gln Lys Ala Ile Asp Gly Val Thr Asn Lys Val Asn Ser Ile  
                   385                                  390                                  395                                  400  
 Ile Asp Lys Met Asn Thr Gln Phe Glu Ala Val Gly Arg Glu Phe Asn  
                                   405                                  410                                  415  
 Asn Leu Glu Arg Arg Ile Glu Asn Leu Asn Lys Lys Met Glu Asp Gly  
                   420                                  425                                  430  
 Phe Leu Asp Val Trp Thr Tyr Asn Ala Glu Leu Leu Val Leu Met Glu  
                   435                                  440                                  445  
 Asn Glu Arg Thr Leu Asp Phe His Asp Ser Asn Val Lys Asn Leu Tyr  
                   450                                  455                                  460  
 Asp Lys Val Arg Leu Gln Leu Arg Asp Asn Ala Lys Glu Leu Gly Asn  
                   465                                  470                                  475                                  480  
 Gly Cys Phe Glu Phe Tyr His Lys Cys Asp Asn Glu Cys Met Glu Ser  
                                   485                                  490                                  495  
 Val Arg Asn Gly Thr Tyr Asp Tyr Pro Gln Tyr Ser Glu Glu Ala Arg  
                   500                                  505                                  510  
 Leu Lys Arg Glu Glu Ile Ser Gly Val Lys Leu Glu Ser Ile Gly Thr  
                   515                                  520                                  525  
 Tyr Gln Ile Leu Ser Ile Tyr Ser Thr Val Ala Ser Ser Leu Ala Leu  
                   530                                  535                                  540  
 Ala Ile Met Val Ala Gly Leu Ser Leu Trp Met Cys Ser Asn Gly Ser  
                   545                                  550                                  555                                  560  
 Leu Gln Cys Arg Ile Cys Ile  
                                   565

<210> SEQ ID NO 56  
 <211> LENGTH: 568  
 <212> TYPE: PRT  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Clone

<400> SEQUENCE: 56

Met Glu Lys Ile Val Leu Leu Phe Ala Ile Val Ser Leu Val Lys Ser  
 1                  5                                  10                                  15  
 Asp Gln Ile Cys Ile Gly Tyr His Ala Asn Asn Ser Thr Glu Gln Val  
                   20                                  25                                  30  
 Asp Thr Ile Met Glu Lys Asn Val Thr Val Thr His Ala Gln Asp Ile  
                   35                                  40                                  45  
 Leu Glu Lys Thr His Asn Gly Lys Leu Cys Asp Leu Asp Gly Val Lys  
                   50                                  55                                  60  
 Pro Leu Ile Leu Arg Asp Cys Ser Val Ala Gly Trp Leu Leu Gly Asn  
                   65                                  70                                  75                                  80  
 Pro Met Cys Asp Glu Phe Ile Asn Val Pro Glu Trp Ser Tyr Ile Val  
                   85                                  90                                  95  
 Glu Lys Ala Asn Pro Val Asn Asp Leu Cys Tyr Pro Gly Asp Phe Asn  
                   100                                  105                                  110  
 Asp Tyr Glu Glu Leu Lys His Leu Leu Ser Arg Ile Asn His Phe Glu  
                   115                                  120                                  125

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Lys Ile Gln Ile Ile Pro Lys Ser Ser Trp Ser Ser His Glu Ala Ser  
 130 135 140  
 Leu Gly Val Ser Ser Ala Cys Pro Tyr Gln Gly Lys Ser Ser Phe Phe  
 145 150 155 160  
 Arg Asn Val Val Trp Leu Ile Lys Lys Asn Ser Thr Tyr Pro Thr Ile  
 165 170 175  
 Lys Arg Ser Tyr Asn Asn Thr Asn Gln Glu Asp Leu Leu Val Leu Trp  
 180 185 190  
 Gly Ile His His Pro Asn Asp Ala Ala Glu Gln Thr Lys Leu Tyr Gln  
 195 200 205  
 Asn Pro Thr Thr Tyr Ile Ser Val Gly Thr Ser Thr Leu Asn Gln Arg  
 210 215 220  
 Leu Val Pro Arg Ile Ala Thr Arg Ser Lys Val Asn Gly Gln Ser Gly  
 225 230 235 240  
 Arg Met Glu Phe Phe Trp Thr Ile Leu Lys Pro Asn Asp Ala Ile Asn  
 245 250 255  
 Phe Glu Ser Asn Gly Asn Phe Ile Ala Pro Glu Tyr Ala Tyr Lys Ile  
 260 265 270  
 Val Lys Lys Gly Asp Ser Thr Ile Met Lys Ser Glu Leu Glu Tyr Gly  
 275 280 285  
 Asn Cys Asn Thr Lys Cys Gln Thr Pro Met Gly Ala Ile Asn Ser Ser  
 290 295 300  
 Met Pro Phe His Asn Ile His Pro Leu Thr Ile Gly Glu Cys Pro Lys  
 305 310 315 320  
 Tyr Val Lys Ser Asn Arg Leu Val Leu Ala Thr Gly Leu Arg Asn Ser  
 325 330 335  
 Pro Gln Arg Glu Arg Arg Arg Lys Lys Arg Gly Leu Phe Gly Ala Ile  
 340 345 350  
 Ala Gly Phe Ile Glu Gly Gly Trp Gln Gly Met Val Asp Gly Trp Tyr  
 355 360 365  
 Gly Tyr His His Ser Asn Glu Gln Gly Ser Gly Tyr Ala Ala Asp Lys  
 370 375 380  
 Glu Ser Thr Gln Lys Ala Ile Asp Gly Val Thr Asn Lys Val Asn Ser  
 385 390 395 400  
 Ile Ile Asp Lys Met Asn Thr Gln Phe Glu Ala Val Gly Arg Glu Phe  
 405 410 415  
 Asn Asn Leu Glu Arg Arg Ile Glu Asn Leu Asn Lys Lys Met Glu Asp  
 420 425 430  
 Gly Phe Leu Asp Val Trp Thr Tyr Asn Ala Glu Leu Leu Val Leu Met  
 435 440 445  
 Glu Asn Glu Arg Thr Leu Asp Phe His Asp Ser Asn Val Lys Asn Leu  
 450 455 460  
 Tyr Asp Lys Val Arg Leu Gln Leu Arg Asp Asn Ala Lys Glu Leu Gly  
 465 470 475 480  
 Asn Gly Cys Phe Glu Phe Tyr His Lys Cys Asp Asn Glu Cys Met Glu  
 485 490 495  
 Ser Val Arg Asn Gly Thr Tyr Asp Tyr Pro Gln Tyr Ser Glu Glu Ala  
 500 505 510  
 Arg Leu Lys Arg Glu Glu Ile Ser Gly Val Lys Leu Glu Ser Ile Gly  
 515 520 525  
 Ile Tyr Gln Ile Leu Ser Ile Tyr Ser Thr Val Ala Ser Ser Leu Ala  
 530 535 540

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Leu Ala Ile Met Val Ala Gly Leu Ser Leu Trp Met Cys Ser Asn Gly  
545 550 555 560

Ser Leu Gln Cys Arg Ile Cys Ile  
565

<210> SEQ ID NO 57  
<211> LENGTH: 566  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: Clone

<400> SEQUENCE: 57

Met Ile Ala Ile Ile Val Ile Ala Ile Leu Ala Ala Ala Gly Lys Ser  
1 5 10 15

Asp Lys Ile Cys Ile Gly Tyr His Ala Asn Asn Ser Thr Thr Gln Val  
20 25 30

Asp Thr Ile Leu Glu Lys Asn Val Thr Val Thr His Ser Ile Glu Leu  
35 40 45

Leu Glu Asn Gln Lys Glu Glu Arg Phe Cys Lys Ile Leu Asn Lys Ala  
50 55 60

Pro Leu Asp Leu Arg Glu Cys Thr Ile Glu Gly Trp Ile Leu Gly Asn  
65 70 75 80

Pro Gln Cys Asp Leu Leu Leu Gly Asp Gln Ser Trp Ser Tyr Ile Val  
85 90 95

Glu Arg Pro Thr Ala Gln Asn Gly Ile Cys Tyr Pro Gly Thr Leu Asn  
100 105 110

Glu Val Glu Glu Leu Arg Ala Leu Ile Gly Ser Gly Glu Arg Val Glu  
115 120 125

Arg Phe Glu Met Phe Pro Gln Ser Thr Trp Gln Gly Val Asp Thr Asn  
130 135 140

Ser Gly Thr Thr Arg Ser Cys Pro Tyr Ser Thr Gly Ala Ser Phe Tyr  
145 150 155 160

Arg Asn Leu Leu Trp Ile Ile Lys Thr Lys Thr Ala Glu Tyr Pro Val  
165 170 175

Ile Lys Gly Ile Tyr Asn Asn Thr Gly Thr Gln Pro Ile Leu Tyr Phe  
180 185 190

Trp Gly Val His His Pro Pro Asn Thr Asp Glu Gln Asp Thr Leu Tyr  
195 200 205

Gly Ser Gly Asp Arg Tyr Val Arg Met Gly Thr Glu Ser Met Asn Phe  
210 215 220

Ala Lys Ser Pro Glu Ile Ala Ala Arg Pro Ala Val Asn Gly Gln Arg  
225 230 235 240

Gly Arg Ile Asp Tyr Tyr Trp Ser Val Leu Lys Pro Gly Glu Thr Leu  
245 250 255

Asn Val Glu Ser Asn Gly Asn Leu Ile Ala Pro Trp Tyr Ala Tyr Lys  
260 265 270

Phe Val Asn Thr Asn Ser Lys Gly Ala Val Phe Arg Ser Asp Leu Pro  
275 280 285

Ile Glu Asn Cys Asp Ala Thr Cys Gln Thr Ile Ala Gly Val Leu Arg  
290 295 300

Thr Asn Lys Thr Phe Gln Asn Val Ser Pro Leu Trp Ile Gly Glu Cys  
305 310 315 320

Pro Lys Tyr Val Lys Ser Glu Ser Leu Arg Leu Ala Thr Gly Leu Arg  
325 330 335

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Asn Val Pro Gln Ile Glu Thr Arg Gly Leu Phe Gly Ala Ile Ala Gly
      340                               345           350

Phe Ile Glu Gly Gly Trp Thr Gly Met Ile Asp Gly Trp Tyr Gly Tyr
      355                               360           365

His His Glu Asn Ser Gln Gly Ser Gly Tyr Ala Ala Asp Arg Glu Ser
      370                               375           380

Thr Gln Lys Ala Val Asn Arg Ile Thr Asn Lys Val Asn Ser Ile Ile
      385                               390           395           400

Asn Lys Met Asn Thr Gln Phe Glu Ala Val Asp His Glu Phe Ser Asn
      405                               410           415

Leu Glu Arg Arg Ile Asp Asn Leu Asn Lys Arg Met Gln Asp Gly Phe
      420                               425           430

Leu Asp Val Trp Thr Tyr Asn Ala Glu Leu Leu Val Leu Leu Glu Asn
      435                               440           445

Glu Arg Thr Leu Asp Met His Asp Ala Asn Val Lys Asn Leu His Glu
      450                               455           460

Lys Val Lys Ser Gln Leu Arg Asp Asn Ala Thr Ile Leu Gly Asn Gly
      465                               470           475           480

Cys Phe Glu Phe Trp His Lys Cys Asp Asn Glu Cys Ile Glu Ser Val
      485                               490           495

Lys Asn Gly Thr Tyr Asp Tyr Pro Lys Tyr Gln Thr Glu Ser Lys Leu
      500                               505           510

Asn Arg Leu Lys Ile Glu Ser Val Lys Leu Glu Asn Leu Gly Val Tyr
      515                               520           525

Gln Ile Leu Ala Ile Tyr Ser Thr Val Ser Ser Ser Leu Val Leu Val
      530                               535           540

Gly Leu Ile Met Ala Met Gly Leu Trp Met Cys Ser Asn Gly Ser Met
      545                               550           555           560

Gln Cys Arg Ile Cys Ile
      565

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&lt;210&gt; SEQ ID NO 58

&lt;211&gt; LENGTH: 570

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Clone

&lt;400&gt; SEQUENCE: 58

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Met Asn Thr Gln Ile Leu Ile Leu Ala Thr Ser Ala Phe Phe Tyr Val
  1      5      10      15

Arg Ala Asp Lys Ile Cys Leu Gly His His Ala Val Ser Asn Gly Thr
      20      25      30

Lys Val Asp Thr Leu Thr Glu Lys Gly Ile Glu Val Val Asn Ala Thr
      35      40      45

Glu Thr Val Glu Gln Thr Asn Ile Pro Lys Ile Cys Ser Lys Gly Lys
      50      55      60

Gln Thr Val Asp Leu Gly Gln Cys Gly Leu Leu Gly Thr Val Ile Gly
      65      70      75      80

Pro Pro Gln Cys Asp Gln Phe Leu Glu Phe Ser Ala Asn Leu Ile Val
      85      90      95

Glu Arg Arg Glu Gly Asn Asp Ile Cys Tyr Pro Gly Lys Phe Asp Asn
      100     105     110

Glu Glu Thr Leu Arg Lys Ile Leu Arg Lys Ser Gly Gly Ile Lys Lys
      115     120     125

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Glu Asn Met Gly Phe Thr Tyr Thr Gly Val Arg Thr Asn Gly Glu Thr  
 130 135 140  
 Ser Ala Cys Arg Arg Ser Arg Ser Ser Phe Tyr Ala Glu Met Lys Trp  
 145 150 155 160  
 Leu Leu Ser Ser Thr Asp Asn Gly Thr Phe Pro Gln Met Thr Lys Ser  
 165 170 175  
 Tyr Lys Asn Thr Lys Lys Val Pro Ala Leu Ile Ile Trp Gly Ile His  
 180 185 190  
 His Ser Gly Ser Thr Thr Glu Gln Thr Arg Leu Tyr Gly Ser Gly Asn  
 195 200 205  
 Lys Leu Ile Thr Val Trp Ser Ser Lys Tyr Gln Gln Ser Phe Val Pro  
 210 215 220  
 Asn Pro Gly Pro Arg Pro Gln Met Asn Gly Gln Ser Gly Arg Ile Asp  
 225 230 235 240  
 Phe His Trp Leu Met Leu Asp Pro Asn Asp Thr Val Thr Phe Ser Phe  
 245 250 255  
 Asn Gly Ala Phe Ile Ala Pro Asp Arg Ala Ser Phe Leu Arg Gly Lys  
 260 265 270  
 Ser Leu Gly Ile Gln Ser Asp Ala Gln Leu Asp Asn Asn Cys Glu Gly  
 275 280 285  
 Glu Cys Tyr His Ile Gly Gly Thr Ile Ile Ser Asn Leu Pro Phe Gln  
 290 295 300  
 Asn Ile Asn Ser Arg Ala Ile Gly Lys Cys Pro Arg Tyr Val Lys Gln  
 305 310 315 320  
 Lys Ser Leu Met Leu Ala Thr Gly Met Lys Asn Val Pro Glu Ala Pro  
 325 330 335  
 Ala His Lys Gln Leu Thr His His Met Arg Lys Lys Arg Gly Leu Phe  
 340 345 350  
 Gly Ala Ile Ala Gly Phe Ile Glu Asn Gly Trp Glu Gly Leu Ile Asp  
 355 360 365  
 Gly Trp Tyr Gly Tyr Lys His Gln Asn Ala Gln Gly Glu Gly Thr Ala  
 370 375 380  
 Ala Asp Tyr Lys Ser Thr Gln Ser Ala Ile Asn Gln Ile Thr Gly Lys  
 385 390 395 400  
 Leu Asn Arg Leu Ile Glu Lys Thr Asn Gln Gln Phe Glu Leu Ile Asp  
 405 410 415  
 Asn Glu Phe Asn Glu Ile Glu Lys Gln Ile Gly Asn Val Ile Asn Trp  
 420 425 430  
 Thr Arg Asp Ser Ile Ile Glu Val Trp Ser Tyr Asn Ala Glu Phe Leu  
 435 440 445  
 Val Ala Val Glu Asn Gln His Thr Ile Asp Leu Thr Asp Ser Glu Met  
 450 455 460  
 Asn Lys Leu Tyr Glu Lys Val Arg Arg Gln Leu Arg Glu Asn Ala Glu  
 465 470 475 480  
 Glu Asp Gly Asn Gly Cys Phe Glu Ile Phe His Gln Cys Asp Asn Asp  
 485 490 495  
 Cys Met Ala Ser Ile Arg Asn Asn Thr Tyr Asp His Lys Lys Tyr Arg  
 500 505 510  
 Lys Glu Ala Ile Gln Asn Arg Ile Gln Ile Asp Ala Val Lys Leu Ser  
 515 520 525  
 Ser Gly Tyr Lys Asp Ile Ile Leu Trp Phe Ser Phe Gly Ala Ser Cys  
 530 535 540  
 Phe Leu Phe Leu Ala Ile Ala Met Gly Leu Val Phe Ile Cys Ile Lys

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545	550	555	560
Asn Gly Asn Met Arg Cys Thr Ile Cys Ile			
	565	570	
<210> SEQ ID NO 59			
<211> LENGTH: 560			
<212> TYPE: PRT			
<213> ORGANISM: Artificial Sequence			
<220> FEATURE:			
<223> OTHER INFORMATION: Clone			
<400> SEQUENCE: 59			
Met Glu Thr Ile Ser Leu Ile Thr Ile Leu Leu Val Val Thr Ala Ser			
1	5	10	15
Asn Ala Asp Lys Ile Cys Ile Gly His Gln Ser Thr Asn Ser Thr Glu			
	20	25	30
Thr Val Asp Thr Leu Thr Glu Thr Asn Val Pro Val Thr His Ala Lys			
	35	40	45
Glu Leu Leu His Thr Glu His Asn Gly Met Leu Cys Ala Thr Ser Leu			
	50	55	60
Gly His Pro Leu Ile Leu Asp Thr Cys Thr Ile Glu Gly Leu Val Tyr			
65	70	75	80
Gly Asn Pro Ser Cys Asp Leu Leu Leu Gly Gly Arg Glu Trp Ser Tyr			
	85	90	95
Ile Val Glu Arg Ser Ser Ala Val Asn Gly Thr Cys Tyr Pro Gly Asn			
	100	105	110
Val Glu Asn Leu Glu Glu Leu Arg Thr Leu Phe Ser Ser Ala Ser Ser			
	115	120	125
Tyr Gln Arg Ile Gln Ile Phe Pro Asp Thr Thr Trp Asn Val Thr Tyr			
130	135	140	
Thr Gly Thr Ser Arg Ala Cys Ser Gly Ser Phe Tyr Arg Ser Met Arg			
145	150	155	160
Trp Leu Thr Gln Lys Ser Gly Phe Tyr Pro Val Gln Asp Ala Gln Tyr			
	165	170	175
Thr Asn Asn Arg Gly Lys Ser Ile Leu Phe Val Trp Gly Ile His His			
	180	185	190
Pro Pro Thr Tyr Thr Glu Gln Thr Asn Leu Tyr Ile Arg Asn Asp Thr			
	195	200	205
Thr Thr Ser Val Thr Thr Glu Asp Leu Asn Arg Thr Phe Lys Pro Val			
210	215	220	
Ile Gly Pro Arg Pro Leu Val Asn Gly Leu Gln Gly Arg Ile Asp Tyr			
225	230	235	240
Tyr Trp Ser Val Leu Lys Pro Gly Gln Thr Leu Arg Val Arg Ser Asn			
	245	250	255
Gly Asn Leu Ile Ala Pro Trp Tyr Gly His Val Leu Ser Gly Gly Ser			
	260	265	270
His Gly Arg Ile Leu Lys Thr Asp Leu Lys Gly Gly Asn Cys Val Val			
	275	280	285
Gln Cys Gln Thr Glu Lys Gly Gly Leu Asn Ser Thr Leu Pro Phe His			
	290	295	300
Asn Ile Ser Lys Tyr Ala Phe Gly Thr Cys Pro Lys Tyr Val Arg Val			
305	310	315	320
Asn Ser Leu Lys Leu Ala Val Gly Leu Arg Asn Val Pro Ala Arg Ser			
	325	330	335
Ser Arg Gly Leu Phe Gly Ala Ile Ala Gly Phe Ile Glu Gly Gly Trp			

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Pro Gly	Leu Val	Ala Gly	Trp Tyr	Gly Phe	Gln His	Ser Asn	Asp Gln								
	355		360			365									
Gly Val	Gly Met	Ala Ala	Asp Arg	Asp Ser	Thr Gln	Lys Ala	Ile Asp								
	370		375			380									
Lys Ile	Thr Ser	Lys Val	Asn Asn	Ile Val	Asp Lys	Met Asn	Lys Gln								
	385		390			395									
Tyr Glu	Ile Ile	Asp His	Glu Phe	Ser Glu	Val Glu	Thr Arg	Leu Asn								
		405			410		415								
Met Ile	Asn Asn	Lys Ile	Asp Asp	Gln Ile	Gln Asp	Val Trp	Ala Tyr								
		420			425		430								
Asn Ala	Glu Leu	Leu Val	Leu Leu	Glu Asn	Gln Lys	Thr Leu	Asp Glu								
		435			440		445								
His Asp	Ala Asn	Val Asn	Asn Asn	Leu Tyr	Asn Lys	Val Lys	Arg Ala	Leu							
		450			455		460								
Gly Ser	Asn Ala	Met Glu	Asp Gly	Lys Gly	Cys Phe	Glu Leu	Tyr His								
		465			470		480								
Lys Cys	Asp Asp	Gln Cys	Met Glu	Thr Ile	Arg Asn	Gly Thr	Tyr Asn								
		485			490		495								
Arg Arg	Lys Tyr	Arg Glu	Glu Ser	Arg Leu	Glu Arg	Gln Lys	Ile Glu								
		500			505		510								
Gly Val	Lys Leu	Glu Ser	Glu Gly	Thr Tyr	Lys Ile	Leu Thr	Ile Tyr								
		515			520		525								
Ser Thr	Val Ala	Ser Ser	Leu Val	Leu Ala	Met Gly	Phe Ala	Ala Phe								
		530			535		540								
Leu Phe	Trp Ala	Met Ser	Asn Asn	Gly Ser	Cys Arg	Cys Asn	Ile Cys	Ile							
		545			550		555								560

&lt;210&gt; SEQ ID NO 60

&lt;211&gt; LENGTH: 3111

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Expression Cassette

&lt;400&gt; SEQUENCE: 60

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agaggtaccc cgggctggta tatttatatg ttgtcaaata actcaaaaac cataaaagtt    60
taagttagca agtgtgtaca tttttacttg aacaaaaata ttcacctact actgttataa    120
atcattatta aacattagag taaagaaata tggatgataa gaacaagagt agtgatattt    180
tgacaacaat tttgttgcaa catttgagaa aatthttgtg ttctctcttt tcattgggtca    240
aaaacaatag agagagaaaa aggaagaggg agaataaaaa cataatgtga gtatgagaga    300
gaaagtgtga caaaagtgtg accaaaatag ttgtacaaat atcattgagg aatthtgaaa    360
aagctacaca aataagggtt aattgctgta aataaataag gatgacgcat tagagagatg    420
taccattaga gaatttttgg caagtcatta aaaagaaaga ataaattatt tttaaaatta    480
aaagttgagt catttgatta aacatgtgat tatttaatga attgatgaaa gagttggatt    540
aaagttgat tagtaattag aatthttgtg caaatttaat ttgacatttg atcttttcct    600
atatattgcc ccatagagtc agttaactca tttttatatt tcatagatca aataagagaa    660
ataacggtat attaatccct ccaaaaaaaaa aaaacggtat atttactaaa aaatctaagc    720
cacgtaggag gataacagga tccccgtagg aggataacat ccaatccaac caatcacaac    780
aatcctgatg agataacca cttaagccc acgcatctgt ggcacatcta cattatctaa    840

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atcacacatt cttccacaca tctgagccac acaaaaacca atccacatct ttatcaccca 900
ttctataaaa aatcacactt tgtgagtcta cactttgatt cccttcaaac acatacaaaag 960
agaagagact aattaattaa ttaatcatct tgagagaaaa tggagaaaaat agtgcttctt 1020
cttgcaatag tcagtcttgt taaaagtgat cagatttgca ttggttacca tgcaaacaaat 1080
tcaacagagc aggttgacac aatcatggaa aagaacgtta ctgttacaca tgcccaagac 1140
atactggaaa agacacacaa cgggaagctc tgcgatctag atggagtga gaccttaatt 1200
ttaagagatt gtagttagc tggatggctc ctcgggaacc caatgtgtga cgaattcatc 1260
aatgtaccgg aatggctta catagtggag aaggccaatc caaccaatga cctctgttac 1320
ccaggaggtt tcaacgacta tgaagaactg aaacacctat tgagcagaat aaaccatttt 1380
gagaaaattc aatcatccc caaaagtctt tggccgatc atgaagcctc atcaggagt 1440
agctcagcat gtccatacct ggggaagctc tccttttta gaaatgtgg atggcttatc 1500
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caagttcaat agattaataa tggaaatctc agttatcgaa attcattaac aatcaactta 3060
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&lt;210&gt; SEQ ID NO 61

&lt;211&gt; LENGTH: 3123

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<212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Expression Cassette  
  
 <400> SEQUENCE: 61

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taagttagca	agtgtgtaca	ttttacttg	aacaaaaata	ttcacctact	actgttataa	120
atcattatta	aacattagag	taaagaata	tggatgataa	gaacaagagt	agtgatattt	180
tgacaacaat	tttgtgcaa	catttgagaa	aattttgttg	ttctctcttt	tcattggtea	240
aaaacaatag	agagagaaaa	aggaagagg	agaataaaaa	cataatgtga	gtatgagaga	300
gaaagttgta	caaaagttgt	accaaaatag	ttgtacaaat	atcattgagg	aatttgacaa	360
aagctacaca	aataagggtt	aattgctgta	aataaataag	gatgacgcat	tagagagatg	420
taccattaga	gaatttttgg	caagtcatta	aaaagaaaga	ataaattatt	ttaaaaatta	480
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aaagttgat	tagtaattag	aatttgggtg	caaatttaat	tgacatttg	atctttctct	600
atatattgoc	ccatagagtc	agttaactca	ttttatatt	tcatagatca	aataagagaa	660
ataacggtat	attaatccct	ccaaaaaaa	aaaacggtat	atttactaaa	aaatctaagc	720
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ggaagaatca	actactactg	gactctgctg	gaacctgggg	atacaataat	atttgaggca	1800
aatgaaatc	taatagcgcc	atggatgct	tttgcactga	gtagaggctt	tggatcagga	1860
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gctataaaca	gcagtcttcc	ttccagaat	gtacaccag	tcacaatagg	agagtgtcca	1980
aagtatgtca	ggagtgcaaa	attaaggatg	gttacaggac	taaggaacat	cccatccatt	2040
caatccagag	gtttgtttgg	agccattgcc	ggtttcattg	aaggggggtg	gactggaatg	2100
gtagatgggt	ggtatgggta	tcatcatcag	aatgagcaag	gatctggcta	tgctgcagat	2160

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caaaaaagta cacaaaatgc cattaacggg attacaaaca aggtcaattc tgtaattgag	2220
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gaaaacttaa ataaaaaagt tgatgatggg tttctagaca tttggacata taatgcagaa	2340
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ctgtatgaga aagtaaaaag ccaattaaag aataatgcca aagaaatagg aaacgggtgt	2460
tttgagttct atcacaagtg taacaatgaa tgcattggaga gtgtgaaaaa tggtagctat	2520
gactatccaa aatattccga agaatacaag ttaaacaggg agaaaattga tggagtgaaa	2580
ttggaatcaa tgggagtata ccgattctg gcgactact caactgtcgc cagttccctg	2640
gttcttttgg tctccctggg ggcaatcagc tttctggatg gttccaatgg gtctttgcag	2700
tgtagaatat gcattctaaga gctctaagtt aaaatgcttc ttcgtctcct atttataata	2760
tggtttgta ttgttaattt tgttcttgta gaagagctta attaatcgtt gttggtatga	2820
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caaatatatg gtcaagtcca atagattaat aatggaaata tcagttatcg aaattcatta	3060
acaatcaact taacgttatt aactactaat tttatatcat cccctttgat aaatgatagt	3120
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&lt;210&gt; SEQ ID NO 62

&lt;211&gt; LENGTH: 3088

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Expression Cassette

&lt;400&gt; SEQUENCE: 62

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ttagagtaaa gaaatatgga tgataagaac aagagtagtg atatdddgac acaatdddg	180
ttgcaacatt tgagaaaatt ttgtdgttct ctctdddcat tggtdcaaaa caatagagag	240
agaaaaagga agagggagaa taaaaacata atgtgagtat gagagagaaa gtdgtacaaa	300
agtdgtacca aaatagtdgt acaaatatca ttgaggaatt tgacaaaagc tacacaaata	360
agggtdaatt gctgtaaaata aataaggatg acgcattaga gagatgtacc attagagaat	420
tdtdggcaag tcattaaaaa gaaagaataa attatdddta aaattdaaaag ttagtdcatt	480
tgattaaaca tgtgattatt taatgaattg atgaaagagt tggattaaaag ttdgtattagt	540
aattagaatt tggtdgtcaaa ttdaatttdga catttdgatct ttdcctatat attgcccct	600
agagtcagtt aactcatttd tatattdcat agatcaataa agagaaataa cggtdatatta	660
atccctccaa aaaaaaaaaa cggtdatatt actaaaaaat ctaagccacg taggaggata	720
acaggatccc cgtaggagga taacatccaa tccaaccaat cacacaatc ctgatgagat	780
aaccacttdt aagcccacgc atctgtggca catctacatt atctaaatca cacattcttc	840
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acacttdgtg agtdctactt ttgattcctc tcaaacacat acaagagaa gagactaatt	960
aattaattda tcatcttdgag agaaaatgaa agtdaaaacta ctgtdcctgt tatgacatt	1020
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tgcttatgtc tctgtagtgt cttcacatta tagcagaaaa ttcaccccag aaatagccaa 1680
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&lt;210&gt; SEQ ID NO 63

&lt;211&gt; LENGTH: 3102

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Expression Cassette

&lt;400&gt; SEQUENCE: 63

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atcattatta aacattagag taaagaaata tggatgataa gaacaagagt agtgatattt	180
tgacaacaat tttgttgcaa catttgagaa aatthttgtg ttctctcttt tcattggca	240
aaaacaatag agagagaaaa aggaagaggg agaataaaaa cataatgtga gtatgagaga	300
gaaagtgtga caaaagtgtg accaaaatag ttgtacaaat atcattgagg aatthtgaca	360
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atatattgcc ccatagagtc agttaactca tttttatatt tcatagatca aataagagaa	660
ataacgggat attaatoct ccaaaaaaaaa aaacgggtat atttactaaa aaatctaagc	720
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ccagaaatag ccaaaagacc caaagtaaga gatcaagaag gaagaatcaa ctactactgg	1740
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atggatgaat gtgatgcgaa gtgccaacaa cctcagggag ctataaacag cagtcttct	1920
ttccagaatg tacacctgt cacaatagga gagtgtccaa agtatgtcag gagtgcaaaa	1980
ttaaggatgg ttacaggact aaggaacatc ccatccattc aatccagagg tttgtttgga	2040
gccattgcg gtttcattga aggggggtgg actggaatgg tagatggttg gtatggttat	2100
catcatcaga atgagcaagg atctggctat gctgcagatc aaaaaagcac acaaatgcc	2160
attaatggga ttacaaacaa ggtcaattct gtaattgaga aaatgaacac tcaattcaca	2220
gctgtgggca aagagttaa caaattggaa agaaggatgg aaaacttaaa taaaaagtt	2280
gatgatgggt ttatagacat ttggacatat aatgcagaat tgttggttct actgaaaaat	2340
gaaaggactt tggatttoca tgactccaat gtgaagaatc tgatgagaa agtaaaaagc	2400

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gaatcaaagt taaacagga gaaaattgat ggagtgaat tggaatcaat gggagtctat	2580
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&lt;210&gt; SEQ ID NO 64

&lt;211&gt; LENGTH: 3093

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Expression Cassette

&lt;400&gt; SEQUENCE: 64

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atcattatta aacattagag taaagaaata tggatgataa gaacaagagt agtgatattt	180
tgacaacaat tttgttcaa catttgagaa aattttgttg ttctctcttt tcattggtca	240
aaaacaatag agagagaaaa aggaagaggg agaataaaaa cataatgtga gtatgagaga	300
gaaagttgta caaaagttgt accaaaatag ttgtacaaat atcattgagg aatttgacia	360
aagctacaca aataaggggt aattgtctgta aataaataag gatgacgcat tagagagatg	420
taccattaga gaatttttgg caagtcatta aaaagaaaga ataaattatt tttaaaatta	480
aaagttgagt catttgatta aacatgtgat tatttaatga attgatgaaa gagttggatt	540
aaagttgat tagtaattag aatttgggtg caaatttaat ttgacatttg atcttttctc	600
atatattgcc ccatagagtc agttaactca tttttatatt tcatagatca aataagagaa	660
ataacggtat attaatccct ccaaaaaaaa aaaacggtat atttactaaa aaatctaagc	720
cacgtaggag gataacagga tccccgtagg aggataacat ccaatccaac caatcacaac	780
aatcctgatg agataaccca ctttaagccc acgcatctgt ggcacatcta cattatctaa	840
atcacacatt cttccacaca tctgagccac acaaaaacca atccacatct ttatcaccia	900
ttctataaaa aatcacactt tgtgagtcta cactttgatt cccttcaaac acatacaaa	960
agaagagact aattaattaa ttaatcatct tgagagaaaa tggccatcat ttatctaatt	1020
ctcctgttca cagcagttag aggggaocaa atatgcattg gataccatgc caataattcc	1080
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cttgagaaga ccataacgg aaagttagc aaactaaacg gaatccctcc acttgaacta	1200
ggggactgta gcattgccc atggctcctt ggaaatccag aatgtgatag gcttctaagt	1260
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gaatcaaatt atccgggtgc caaaggatcg tacaacaata caagcggaga acaaatgcta 1560
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gcaacaaggc ctaaagtgaa tggactagga agtagaatgg agttctcttg gaccctattg 1740
gatatgtggg acaccataaa ttttgagagt actggtaatc taattgcacc agagtatgga 1800
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tgtgagacca aatgccaaac tcttttggga gcaataaata caacattgcc tttcacaat 1920
gtcccccac tgacaatagg tgagtcccc aaatatgtaa aatcggagaa gttggtctta 1980
gcaacaggac taaggaatgt tcccagatt gaatcaagag gattgtttgg ggcaatagct 2040
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aatgaccagg gatcagggta tgcagcagac aaagaatcca ctcaaaaggc atttgatgga 2160
atcaccaaca aggtaaatc tgtgattgaa aagatgaaca cccaattga agctgttggg 2220
aaagagttca gtaacttaga gagaagactg gagaactga acaaaaagat ggaagacggg 2280
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cttgacttcc atgattctaa tgtcaagaat ctgtatgata aagtcagaat gcagctgaga 2400
gacaacgtca aagaactagg aatggatgt tttgaatctt atcacaatg tgatgatgaa 2460
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ctaaatagaa atgaaatcaa aggggtaaaa ttgagcagca tgggggttta tcaaatcctt 2580
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ttctggatgt gctccaacgg gtctctgcag tgcaggatct gcatatgaga gctctaagtt 2700
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gaagagctta attaactggt gttgttatga aatactattt gtatgagatg aactggtgta 2820
atgtaattca tttacataag tggagtcaga atcagaatgt ttcctccata actaactaga 2880
catgaagacc tgcgcgctac aattgtctta tatttgaaca actaaaattg aacatctttt 2940
gccacaactt tataagtggt taatatagct caaatatag gtcaagttca atagattaat 3000
aatggaaata tcagttatcg aaatcatta acaatcaact taacggtatt aactactaat 3060
tttatatcat cccctttgat aatgatagt aca 3093

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<210> SEQ ID NO 65
<211> LENGTH: 3108
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Expression Cassette

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<400> SEQUENCE: 65

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taagttagca agtgtgtaca tttttacttg aacaaaaata ttcacctact actgttataa 120
atcattatta aacattagag taaagaaata tggatgataa gaacaagagt agtgatattt 180
tgacaacaat tttgttgcaa catttgagaa aatttgttg ttctctcttt tcattggtca 240
aaaacaatag agagagaaaa aggaagaggg agaataaaaa cataatgtga gtatgagaga 300

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gaaagttgta	caaaagttgt	accaaataag	ttgtacaaat	atcattgagg	aatTTgacaa	360
aagctacaca	aataaggggt	aattgctgta	aataaataag	gatgacgcat	tagagagatg	420
taccattaga	gaatTTTTtg	caagtcatta	aaaagaaaga	ataaattatt	tttaaaatta	480
aaagttgagt	catttgatta	aacatgtgat	tatttaatag	attgatgaaa	gagttggatt	540
aaagttgfat	tagtaattag	aattTggTgt	caaatttaat	ttgacatttg	atcttttctt	600
atatattgcc	ccatagagtc	agTtaactca	tttttatatt	tcatagatca	aataagagaa	660
ataacggfat	attaatccct	ccaaaaaaa	aaaacggfat	atttactaaa	aaatctaagc	720
cacgtaggag	gataacagga	tccccgtagg	aggataacat	ccaatccaac	caatcacaac	780
aatctgatg	agataaccca	cttTaaGCC	acgcatctgt	ggcacatcta	cattatctaa	840
atcacacatt	cttccacaca	tctgagccac	acaaaaacca	atccacatct	ttatcaccca	900
ttctataaaa	aatcacactt	tgtgagtcta	cactttgatt	cccttcaaac	acatacaaaG	960
agaagagact	aattaattaa	ttaatcatct	tgagagaaaa	tggagaaaat	agtgcttctt	1020
cttgcaatag	tcagccttgt	taaaagtgat	cagatttgca	ttggttacca	tgcaaaacaac	1080
tcgacagagc	aggttgacac	aataatggaa	aagaacgtta	ctgttacaca	tgcccaagac	1140
atactggaag	agacacacaa	cgggaagctc	tcgcatctag	atggagtga	gcctctgatt	1200
ttaagagatt	gtagtgtagc	tggatggctc	ctcggaaaac	caatgtgtga	cgagttcatc	1260
aatgtgccgg	aatggcttta	catagtggag	aaggccaacc	cagccaatga	cctctgttac	1320
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gagaaaattc	agatcatccc	caaaagtTct	tggTccgatc	atgaagcctc	atcaggggTc	1440
agctcagcat	gtccatacca	gggaacgcc	tcctttttca	gaaatgtggT	atggcttatc	1500
aaaaagaaca	atacatacc	aacaataaag	agaagctaca	ataataccaa	ccaggaagat	1560
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tatgcataca	aaattgtcaa	gaaaggggac	tcagcaattg	tTaaaagtga	agtggaatat	1860
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gtccttgca	ctgggctcag	aaatagtcct	ctaagagaaa	gaagaagaaa	aagaggacta	2040
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gggtaccacc	atagcaatga	gcagggggagt	gggtacgctg	cagacaaaga	atccactcaa	2160
aaggcaatag	atggagtcc	caataaggtc	aactcgatca	ttgacaaaat	gaacactcag	2220
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cgactacagc	ttagggataa	tgcaaaaggag	ctgggtaacg	gttgtttcga	gttctatcac	2460
aaatgtgata	atgaatgat	ggaaagtgt	agaaacggaa	cgtatgacta	cccgcagtat	2520
tcagaagaag	caagatTaaa	aagagaggaa	ataagtggag	Taaaattgga	atcaatagga	2580
actTaccaaa	tactgtcaat	ttattcaaca	gttgcgagtt	ctctagcact	ggcaatcatg	2640

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gtggctggtc tatctttgtg gatgtgctcc aatgggctcg tacaatgcag aatttgcatt	2700
taagagctct aagttaaaat gcttcttcgt ctctattta taatattggt tgttattggt	2760
aattttgttc ttgtagaaga gcttaattaa tegtgtgtg tatgaaatac tatttgtatg	2820
agatgaactg gtgtaatgta attcatttac ataagtggag tcagaatcag aatgtttcct	2880
ccataactaa ctagacatga agacctgccg cgtacaattg tcttatattt gaacaactaa	2940
aattgaacat cttttgccac aactttataa gtggtaata tagctcaaat atattggtcaa	3000
gttcaataga ttaataatgg aaatatcagt tatcgaaatt cattaacaat caacttaacg	3060
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&lt;210&gt; SEQ ID NO 66

&lt;211&gt; LENGTH: 3111

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Expression Cassette

&lt;400&gt; SEQUENCE: 66

agaggtagcc cgggctggta tttttatag ttgtcaaata actcaaaaac cataaaagt	60
taagttagca agtgtgtaca tttttacttg aacaaaaata ttcacctact actgttataa	120
atcattatta aacattagag taaagaaata tggatgataa gaacaagagt agtgatattt	180
tgacaacaat tttgttcaa catttgagaa aattttgttg ttctctcttt tcattggtca	240
aaaacaatag agagagaaaa aggaagaggg agaataaaaa cataatgtga gtatgagaga	300
gaaagttgta caaaagttgt accaaaatag ttgtacaaat atcattgagg aatttgacaa	360
aagctacaca aataagggtt aattgtctga aataaataag gatgacgcat tagagagatg	420
taccattaga gaatttttgg caagtcatta aaaagaaaga ataaattatt tttaaaatta	480
aaagttgagt catttgatta aacatgtgat ttttaataga attgatgaaa gagttggatt	540
aaagttgat tagtaattag aatttgggtg caaatttaat ttgacatttg atcttttcct	600
atataattgcc ccatagagtc agttaactca tttttatatt tcatagatca aataagagaa	660
ataacggtat attaatccct ccaaaaaaaaa aaaacggtat atttactaaa aaatctaagc	720
cacgtaggag gataacagga tcccctgtag aggataacat ccaatccaac caatcacaac	780
aatcctgatg agataaccca ctttaagccc acgcatctgt ggcacatcta cattatctaa	840
atcacacatt cttccacaca tctgagccac acaaaaacca atccacatct ttatcaccca	900
ttctataaaa aatcacactt tgtgagtcta cactttgatt cccttcaaac acatacaaa	960
agaagagact aattaattaa ttaatcatct tgagagaaaa tggagaaaa agtgcttctt	1020
tttgcaatag tcagtcttgt taaaagtgat cagatttgca ttggttacca tgcaaacac	1080
tcgacagagc aggttgacac aataatggaa aagaacgta ctgttacaca tgcccaagac	1140
atactggaag agacacacaa tgggaagctc tgccatctag atggagtga gcctctaatt	1200
ttgagagatt gtagttagc tggatggctc ctcgaaacc caatgtgtga cgagttcatc	1260
aatgtgccgg aatggtctta catagtggag aaggccaatc cagtcaatga cctctgttac	1320
ccaggggatt tcaatgacta tgaagaattg aaacacctat tgagcagaat aaaccatttt	1380
gagaaaaatc agatcatccc caaaagtctt tgggccagtc atgaagcctc attgggggtc	1440
agctcagcat gtccatacca gggaaagtcc tectttttca gaaatgtggg atggcttate	1500
aaaaagaaca gtacataccc aacaataaag aggagctaca ataataccaa ccaagaagat	1560
cttttggtag tgtgggggat tcaccatcct aatgatgagg cagagcagac aaagctctat	1620

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caaaacccaa ccacctatat ttcggtggg acatctacac taaaccagag attggtacca 1680
agaatagcta ctagatccaa agtaaacggg caaagtggaa ggatggagtt cttctggaca 1740
atthtaaac cgaatgatgc aatcaacttc gagagtaatg gaaatttcat tgctccagaa 1800
tatgcataca aaattgtcaa gaaaggggac tcaacaatta tgaaaagtga attggaatat 1860
ggtaactgca ataccaagtg tcaactcca atgggggcca taaactctag catgccattc 1920
cacaatatac accctctcac catcggggaa tgcccaaat atgtgaaatc aaacagatta 1980
gtccttgcca ctgggctcag aaatagccct caaagagaga gaagaagaaa aaagagagga 2040
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tatgggtacc accatagcaa cgagcagggg agtgggtacg ctgcagacaa agaatccact 2160
caaaaggcaa tagatggagt caccaataag gtcaactcga ttattgacaa aatgaacact 2220
cagtttgagg ccgttggaag ggaatttaac aacttagaaa ggagaataga gaatttaaac 2280
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tattcagaag aagcaagact aaaaagagag gaaataatg gagtaaaatt ggaatcaata 2580
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cctccataac taactagaca tgaagaactg ccgctacaa ttgtcttata tttgaacaac 2940
taaaattgaa catcttttgc cacaacttta taagtggta atatagctca aatataatgg 3000
caagttcaat agattaataa tggaaatc agttatcgaa attcattaac aatcaactta 3060
acgttattaa ctactaattt tatatcatcc cctttgataa atgatagtac a 3111

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<210> SEQ ID NO 67
<211> LENGTH: 3105
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Expression Cassette

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<400> SEQUENCE: 67

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atcattatta aacattagag taaagaaata tggatgataa gaacaagagt agtgatattt 180
tgacaacaat tttgtgcaa catttgagaa aattttgttg ttctctcttt tcattggtca 240
aaaaaatag agagagaaaa aggaagaggg agaataaaaa cataatgtga gtatgagaga 300
gaaagtgtga caaaagtgt accaaaatag ttgtacaaat atcattgagg aatttgacaa 360
aagctacaca aataaggggt aattgctgta aataaataag gatgacgcat tagagagatg 420
taccattaga gaatttttgg caagtcatta aaaagaaaga ataaattatt tttaaaatta 480
aaagttgagt catttgatta aacatgtgat tatttaatga attgatgaaa gagttggatt 540

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aaagttgat tagtaattag aatttgggtg caaatttaat ttgacatttg atcttttcct	600
atatattgcc ccatagagtc agttaactca tttttatatt tcatagatca aataagagaa	660
ataacgggat attaatccct ccaaaaaaaaa aaaacgggat atttactaaa aaatctaagc	720
cacgtaggag gataacagga tccccgtagg aggataacat ccaatccaac caatcacaac	780
aatcctgatg agataacca cttaagccc acgcatctgt ggcacatcta cattatctaa	840
atcacacatt ctccacaca tctgagccac acaaaaaacca atccacatct ttatcaccca	900
ttctataaaa aatcacactt tgtgagtcta cactttgatt cccttcaaac acatacaaag	960
agaagagact aattaattaa ttaatcatct tgagagaaaa tgattgcaat cattgtaata	1020
gcaactactgg cagcagccgg aaagtcagac aagatctgca ttgggtatca tgccaacaat	1080
tcaacaacac aggtagatag gatacttgag aagaatgtga ctgtcacaca ctcaattgaa	1140
ttgctggaat atcagaagga agaagattc tgcaagatat tgaacaaggc ccctctcgac	1200
ttaaggggat gtaccataga gggttggatc ttggggaatc cccaatgoga cctattgctt	1260
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gagagatttg agatgtttcc ccaaaagcacc tggcaaggag ttgacacca cagtggaaca	1440
acaagatcct gcccttattc tactggtgcg tctttctaca gaaacctcct atggataata	1500
aaaaccaaga cagcagaata tccagtaatt aagggaaattt acaacaacac tggaaccag	1560
ccaatcctct atttctgggg tgtgcatcat cctcctaaca ccgacgagca agatactctg	1620
tatggctctg gtgatcgata cgtagaatg ggaactgaaa gcatgaattt tgccaagagt	1680
ccgaaattg cggcaaggcc tgcgtgtaat ggacaaagag gcagaattga ttattattgg	1740
tgggttttaa aaccagggga aaccttgaat gtggaatcta atggaaatct aatcgccct	1800
tggtatgcat acaaatattg caacacaaat agtaaaggag ccgtcttcag gtcagattta	1860
ccaatcgaga actgcatgac cacatgccag actattgcag gggttctaag gaccaataaa	1920
acatttcaga atgtgagtc cctgtggata ggagaatgac ccaatacgt gaaaagtgaa	1980
agtctgagcc ttgcaactgg actaagaaat gttccacaga ttgaaactag aggactctc	2040
ggagctattg cagggtttat tgaaggagga tggactggga tgatagatgg gtggtatggc	2100
tatcaccatg aaaattctca agggtcagga tatgcagcag acagagaaaag cactcaaaag	2160
gctgtaaaac gaattacaaa taaggtcaat tccatcatca acaaaatgaa cacacaattt	2220
gaagctgtcg atcacgaatt ttcaaatctg gagaggagaa ttgacaatct gaacaaaaga	2280
atgcaagatg gatttctgga tgtttggaca tacaatgctg aactgttggt tcttcttgaa	2340
aacgaaagaa cactagacat gcatgacgca aatgtgaaga acctacatga aaaggcaca	2400
tcacaactaa gggacaatgc tacgatctta gggaatggtt gctttgaatt ttggcataag	2460
tgtgacaatg aatgcataga gtctgtcaaa aatggtacat atgactatcc caaataccag	2520
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tttgttcttg tagaagagct taattaatcg ttgtgttat gaaatactat ttgtatgaga	2820
tgaactggtg taatgtaatt catttacata agtggagtca gaatcagaat gtttcctcca	2880
taactaacta gacatgaaga cctgccgctg acaattgtct tatatttgaa caactaaaat	2940

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tgaacatctt ttgccacaac tttataagtg gttaatatag ctcaaatata tggccaagtt	3000
caatagatta ataatggaaa tatcagttat cgaaattcat taacaatcaa cttaacgtta	3060
ttaactacta attttatatc atcccctttg ataaatgata gtaca	3105

<210> SEQ ID NO 68  
 <211> LENGTH: 3087  
 <212> TYPE: DNA  
 <213> ORGANISM: Artificial Sequence  
 <220> FEATURE:  
 <223> OTHER INFORMATION: Expression Cassette

<400> SEQUENCE: 68

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taagttagca agtgtgtaca tttttacttg aacaaaaata ttcacctact actgttataa	120
atcattatta aacattagag taaagaaata tggatgataa gaacaagagt agtgatattt	180
tgacaacaat tttgttgcaa catttgagaa aattttgttg ttctctcttt tcattggtca	240
aaaacaatag agagagaaaa aggaagaggg agaataaaaa cataatgtga gtatgagaga	300
gaaagttgta caaaagttgt accaaaatag ttgtacaaat atcattgagg aatttgacaa	360
aagctacaca aataaggggt aattgctgta aataaataag gatgacgcat tagagagatg	420
taccattaga gaatttttgg caagtcatta aaaagaaaga ataaattatt tttaaaatta	480
aaagttgagt catttgatta aacatgtgat tatttaatga attgatgaaa gagttggatt	540
aaagttgat tagtaattag aatttgggtg caaatttaat ttgacatttg atcttttcct	600
atatattgcc ccatagagtc agttaactca tttttatatt tcatagatca aataagagaa	660
ataacggtat attaatccct ccaaaaaaaaa aaaacggtat atttactaaa aaatctaagc	720
cacgtaggag gataacagga tcccctagg aggataacat ccaatccaac caatcacaac	780
aatcctgatg agataaccoca ctttaagccc acgcatctgt ggcacatcta cattatctaa	840
atcacacatt cttccacaca tctgagccac acaaaaacca atccacatct ttatcaccia	900
ttctataaaa aatcacactt tgtgagtcta cactttgatt cccttcaaac acatacaaa	960
agaagagact aattaattaa ttaatcatct tgagagaaaa tggaaacaat atcactaata	1020
actatactac tagtagtaac agcaagcaat gcagataaaa tctgcatcgg ccaccagtca	1080
acaaactcca cagaaactgt ggacacgcta acagaaacca atgttcctgt gacacatgcc	1140
aaagaattgc tccacacaga gcataatgga atgctgtgtg caacaagcct gggacatccc	1200
ctcattctag acacatgcac tattgaagga ctagtctatg gcaacccttc ttgtgacctg	1260
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agcagagcat gttcaggttc attctacagg agtatgagat ggctgactca aaagagcggg	1500
ttttaccctg ttcaagacgc ccaatacaca aataacaggg gaaagagcat tcttttcgtg	1560
tggggcatac atcaccacc cacctatacc gagcaaaaa atttgtacat aagaaacgac	1620
acaacaacaa gcgtgacaac agaagatttg aataggacct tcaaaccagt gatagggcca	1680
aggccccttg tcaatggtct gcaggaaga attgattatt attggtcggg actaaaacca	1740
ggccaaacat tgcgagtacg atccaatggg aatctaattg ctccatggta tggacacgtt	1800
ctttcaggag ggagccatgg aagaatcctg aagactgatt taaaaggtgg taattgtgta	1860

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gtgcaatgtc agactgaaaa aggtggctta aacagtacat tgccattcca caatatcagt	1920
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ggtctgagga acgtgcctgc tagatcaagt agaggactat ttggagccat agctggattc	2040
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caaggggttg gtatggctgc agatagggat tcaactcaaa aggcaattga taaaataaca	2160
tccaaggatg ataatatagt cgacaagatg aacaagcaat atgaaataat tgatcatgaa	2220
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gacgtatggg catataatgc agaattgcta gtactacttg aaaatcaaaa aacctcgat	2340
gagcatgatg cgaacgtgaa caatctatat aacaaggatg agagggcact gggctccaat	2400
gctatggaag atgggaaagg ctgtttcgag ctataccata aatgtgatga tcagtgcattg	2460
gaaacaattc ggaacgggac ctataatagg agaaagtata gagaggaatc aagactagaa	2520
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gccatgtcca atggatcttg cagatgcaac atttgtatat aagagctcta agttaaagt	2700
cttcttcgtc tcctatttat aatatgggtt gttattgtta atttgttct tgtagaagag	2760
cttaattaat cgttgttgtt atgaaatact atttgtatga gatgaactgg tgtaatgtaa	2820
ttcatttaca taagtggagt cagaatcaga atgtttcctc cataactaac tagacatgaa	2880
gacctgccgc gtacaattgt cttatatattg aacaactaaa attgaacatc ttttgcaca	2940
actttataag tggtaatat agctcaaata tatggtcaag ttcaatagat taataatgga	3000
aatatcagtt atcgaaatc attaacaatc aacttaacgt tattaactac taattttata	3060
tcacccctt tgataaatga tagtaca	3087

&lt;210&gt; SEQ ID NO 69

&lt;211&gt; LENGTH: 3105

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Expression Cassette

&lt;400&gt; SEQUENCE: 69

agaggtaccc cgggctggta tatttatatg ttgtcaaata actcaaaaac cataaaagtt	60
taagttagca agtgtgtaca ttttacttg aacaaaaata ttacactact actgttataa	120
atcattatta aacattagag taaagaaata tggatgataa gaacaagagt agtgatattt	180
tgacaacaat tttgttgcaa catttgagaa aattttgttg ttctctcttt tcattggtca	240
aaaacaatag agagagaaaa aggaagaggg agaataaaaa cataatgtga gtatgagaga	300
gaaagtgtga caaaagtgt accaaaatag ttgtacaaat atcattgagg aatttgacaa	360
aagctacaca aataaggggt aattgctgta aataaataag gatgacgcat tagagagatg	420
taccattaga gaatttttgg caagtcatta aaaagaaaga ataaattatt tttaaaatta	480
aaagttgagt catttgatta aacatgtgat tatttaatga attgatgaaa gagttggatt	540
aaagttgtat tagtaattag aatttggtgt caaatttaat ttgacatttg atcttttcct	600
atatattgcc ccatagagtc agttaactca tttttatatt tcatagatca aataagagaa	660
ataacggat attaatccct ccaaaaaaaaa aaaacggat atttactaaa aaatctaagc	720
cacgtaggag gataacagga tccccgtagg aggataacat ccaatccaac caatcacaac	780
aatctgatg agataaccca cttaaagccc acgcatctgt ggcacatcta cattatctaa	840

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atcacacatt	cttccacaca	tctgagccac	acaaaaacca	atccacatct	ttatcaccca	900
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agaagagact	aattaattaa	ttaatcatct	tgagagaaaa	tgaagactat	cattgctttg	1020
agctacattc	tatgtctggt	tttcaactca	aaacttcccg	gaaatgacaa	cagcacggca	1080
acgctgtgoc	ttgggcacca	tgacgtacca	aacggaacga	tagtgaaaac	aatcacgaat	1140
gaccaaattg	aagttactaa	tgctactgag	ctggttcaga	gttctcctcaac	aggtgaaata	1200
tgcgacagtc	ctcatcagat	ccttgatgga	gaaaactgca	cactaataga	tgctctattg	1260
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aaagcctaca	gcaactgtta	cccttatgat	gtgccggatt	atgcctccct	taggtcacta	1380
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caaaacggaa	caagctctgc	ttgcataagg	agatctaata	acagtctctt	tagtagattg	1500
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agagatgaag	cattaaccaa	ccggttccag	atcaagggcg	ttgagctgaa	gtcaggatac	2580
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gagctctaag	ttaaaatgct	tcttctgtct	ctatttataa	tatggtttgt	tattgttaat	2760
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taactaacta	gacatgaaga	cctgcgcgct	acaattgtct	tataattgaa	caactaaaat	2940
tgaacatctt	ttgccacaac	tttataagtg	gttaatatag	ctcaaatata	tggtcaagtt	3000
caatagatta	ataatggaaa	tatcagttat	cgaaatccat	taacaatcaa	cttaacgtta	3060
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<211> LENGTH: 3105
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Expression Cassette

<400> SEQUENCE: 70
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taagttagca agtgtgtaca tttttacttg aacaaaaata ttcacctact actgttataa    120
atcattatta aacattagag taaagaaata tggatgataa gaacaagagt agtgatattt    180
tgacaacaat tttgttgcaa catttgagaa aattttggtg ttctctcttt tcattggtca    240
aaaacaatag agagagaaaa aggaagaggg agaataaaaa cataatgtga gtatgagaga    300
gaaagtgtga caaaagttgt accaaaatag ttgtacaaat atcattgagg aatttgacaa    360
aagctacaca aataaggggt aattgtctga aataaataag gatgacgcat tagagagatg    420
taccattaga gaatttttgg caagtcatta aaaagaaaga ataaattatt tttaaaatta    480
aaagttgagt catttgatta aacatgtgat tatttaatga attgatgaaa gagttggatt    540
aaagttgat tagtaattag aatttggtgt caaatttaat ttgacatttg atcttttctc    600
atatattgcc ccatagagtc agttaactca tttttatatt tcatagatca aataagagaa    660
ataacggtat attaatccct ccaaaaaaaaa aaaacggtat atttactaaa aaatctaagc    720
cacgtaggag gataaacagga tccccgtagg aggataacat ccaatccaac caatcacaac    780
aatcctgatg agataaccoca ctttaagccc acgcatctgt ggcacatcta cattatctaa    840
atcacacatt cttccacaca tctgagccac acaaaaacca atccacatct ttatcaccca    900
ttctataaaa aatcacactt tgtgagtcta cactttgatt cccttcaaac acatacaaa    960
agaagagact aattaattaa ttaatcatct tgagagaaaa tgaagactat cattgctttg    1020
agctacattc tatgtctggt tttcactcaa aaacttcccg gaaatgacaa cagcacggca    1080
acgctgtgcc ttgggcacca tgcagtacca aacggaacga tagtgaaaac aatcacgaat    1140
gaccaaattg aagttactaa tgctactgag ctggttcaga gttcctcaac aggtggaata    1200
tgcgacagtc ctcacagat ccttgatgga gaaaactgca cactaataga tgctctattg    1260
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gttcctcat cggcacact ggagttaac gatgaaagt tcaattggac tggagtcact    1440
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aattggttga ccacttaaa attcaaatc ccagcattga acgtgactat gccaaaacaat    1560
gaaaaattg acaaattgta catttggggg gttcaccacc cgggtacgga caatgaccaa    1620
atcttctctg atgctcaagc atcaggaaga atcacagtct ctacccaaaag aagccaacaa    1680
actgtaatcc cgaatatcgg atctagacc cagaataagga atatccccag cagaataagc    1740
atctattgga caatagtaaa accgggagac atacttttga ttaacagcac agggaatcta    1800
attgctccta ggggttactt caaaatcga agtgggaaaa gctcaataat gagatcagat    1860
gcacccattg gcaaatgcaa ttctgaatgc atcactccaa atggaagcat tcccaatgac    1920
aaaccatttc aaaatgtaaa caggatcaca tatggggcct gtcccagata tgtaagcaa    1980
aacactctga aattggcaac agggatgcca aatgtaccag aaaaacaaac tagaggcata    2040
tttgccgcaa tcgccgggtt catagaaaat ggttgggagg gaatggtgga tggttggtac    2100
ggttccaggc atcaaaatc tgagggaaata ggacaagcag cagatctcaa aagcactcaa    2160

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gcagcaatca atcaaatcaa tgggaagctg aatagggtga tgggaaaaac caacgagaaa 2220
ttccatcaga ttgaaaaaga gttctcagaa gtagaagggg gaatccagga cctcgagaaa 2280
tatggtgagg aactaaaaat agatctctgg tcatacaacg cggagcttct tgttgccctg 2340
gagaaccaac atacaattga tctaactgac tcagaaatga acaaactggt tgaagaaca 2400
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aaagattgga tactatggat ttcctttgcc atatcatggt ttttgccttg tgttgccttg 2640
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tttgttcttg tagaagagct taattaatcg ttgttgttat gaaatactat ttgtatgaga 2820
tgaactggtg taatgtaatt catttacata agtggagtca gaatcagaat gtttcctcca 2880
taactaacta gacatgaaga cctgccgctg acaattgtct tatatttgaa caactaaaat 2940
tgaacatctt ttgccacaac tttataagtg gttaatatag ctcaaatata tggccaagtt 3000
caatagatta ataatggaaa tatcagttat cgaaattcat taacaatcaa cttaacgtta 3060
ttaactacta attttatatc atcccctttg ataaatgata gtaca 3105

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<210> SEQ ID NO 71
<211> LENGTH: 3117
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Expression Cassette

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<400> SEQUENCE: 71

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atcattatta aacattagag taaagaaata tggatgataa gaacaagagt agtgatattt 180
tgacaacaat tttgttgcaa catttgagaa aattttgttg ttctctcttt tcattgggtca 240
aaaacaatag agagagaaaa aggaagaggg agaataaaaa cataatgtga gtatgagaga 300
gaaagtgtga caaaagtgtg accaaaatag ttgtacaaat atcattgagg aatttgacaa 360
aagctacaca aataaggggtt aattgctgta aataaataag gatgacgcat tagagagatg 420
taccattaga gaattttggg caagtcatta aaaagaaaga ataaattatt tttaaaatta 480
aaagttgagt catttgatta aacatgtgat tatttaatga attgatgaaa gagttggatt 540
aaagttgat tagtaattag aatttgggtg caaatttaat ttgacatttg atcttttctt 600
atatattgcc ccatagagtc agttaactca tttttatatt tcatagatca aataagagaa 660
ataacggtat attaatecct ccaaaaaaaaa aaaacggtat atttactaaa aaatctaagc 720
cacgtaggag gataacagga tccccgtagg aggataacat ccaatccaac caatcacaac 780
aatcctgatg agataaccca ctttaagccc acgcatctgt ggcacatcta cattatctaa 840
atcacacatt cttccacaca tctgagccac acaaaaacca atccacatct ttatcaccca 900
ttctataaaa aatcacactt tgtgagtcta cactttgatt cccttcaaac acatacaaag 960
agaagagact aattaattaa ttaatcatct tgagagaaaa tgaacactca aattctaata 1020
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gtgtctaattg gaaccaaagt agacaccctt actgaaaaag gaatagaagt tgtcaatgca 1140
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gaccttggtc aatgtggatt actagggacc gttattggtc ctcccgaatg tgaccaattt 1260
cttgagttct ctgctaattt aatagttgaa agaaggggag gtaatgacat ttgttatcca 1320
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aaggagaata tgggattcac atataccgga gtgagaacca atggagagac tagcgcatgt 1440
agaaggtcaa gatcttcctt ttatgcagag atgaaatggc ttctatccag cacagacaat 1500
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aataaattga taacagtttg gagttccaaa taccaacaat cttttgtccc aaatcctgga 1680
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gaaatattcc accaatgtga caatgattgc atggccagca ttagaaacaa cacatatgac 2520
cataaaaaat acagaaaaga ggcaatacaa aacagaatcc agattgacgc agtaaagtgt 2580
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atgtgtatat aagagctcta agttaaagt cttcttcgtc tcctatttat aatatggttt 2760
gttattgtta atttgttct tgtagaagag cttaattaat cgttgtgtgt atgaaatact 2820
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aacaactaaa attgaacatc ttttgccaca actttataag tggttaatat agctcaata 3000
tatggtcaag ttcaatagat taataatgga aatatcagtt atcgaaatc attaacaatc 3060
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&lt;210&gt; SEQ ID NO 72

&lt;211&gt; LENGTH: 3162

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Expression Cassette

&lt;400&gt; SEQUENCE: 72

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tgacaacaat	tttgttgcaa	catttgagaa	aattttgttg	ttctctcttt	tcattggtca	240
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gaaagtgtga	caaaagtgtg	accaaaatag	ttgtacaaat	atcattgagg	aatttgacaa	360
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atatattgcc	ccatagagtc	agttaactca	tttttatatt	tcatagatca	aataagagaa	660
ataacggtat	attaatccct	ccaaaaaaaa	aaaacggtat	atttactaaa	aaatctaagc	720
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ctaagcggtg	ccatggatga	actccacaac	gaaatactag	aactagacga	gaaagtggat	2340
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acatcttttg ccacaacttt ataagtgggt aatatagctc aatatatgg tcaagttcaa	3060
tagattaata atgaaaatat cagttatgca aattcattaa caatcaactt aacgttatta	3120
actactaatt ttatatcatc ccctttgata aatgatagta ca	3162

&lt;210&gt; SEQ ID NO 73

&lt;211&gt; LENGTH: 3159

&lt;212&gt; TYPE: DNA

&lt;213&gt; ORGANISM: Artificial Sequence

&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Expression Cassette

&lt;400&gt; SEQUENCE: 73

agaggtaccc cgggctggta ttttatatg ttgtcaaata actcaaaaac cataaaagt	60
taagttagca agtgtgtaca ttttacttg acaaaaaata ttcacctact actgttataa	120
atcattatta aacattagag taaagaaata tggatgataa gaacaagagt agtgatatt	180
tgacaacaat tttgttgcaa catttgagaa aattttgttg ttctctcttt tcattggcca	240
aaaacaatag agagagaaaa aggaagaggg agaataaaaa cataatgtga gtatgagaga	300
gaaagtgtga caaaagtgt accaaaatag ttgtacaaat atcattgagg aatttgacaa	360
aagctacaca aataaggggt aattgctgta aataaataag gatgacgcat tagagagatg	420
taccattaga gaatttttgg caagtcatta aaaagaaaga ataaattatt tttaaaatta	480
aaagttgagt catttgatta aacatgtgat tatttaatga attgatgaaa gagttggatt	540
aaagttgtat tagtaattag aatttgggtg caaatttaat ttgacatttg atcttttcct	600
atatattgcc ccatagagtc agttaactca tttttatatt tcatagatca aataagagaa	660
ataacggtat attaatoctt ccaaaaaaaaa aaaacggtat atttactaaa aaatctaagc	720
cacgtaggag gataacagga tccccgtagg aggataacat ccaatccaac caatcacaac	780
aatctgatg agataacca ctttaagccc acgcatctgt ggcacatcta cattatctaa	840
atcacacatt cttccacaca tctgagccac acaaaaacca atccacatct ttatcaccca	900
ttctataaaa aatcacactt tgtgagtcta cactttgatt cccttcaaac acatacaaag	960
agaagagact aattaattaa ttaatcatct tgagagaaaa tgaaggcaat aattgtacta	1020
ctcatggtag taacatccaa tgcagatcga atctgcaactg gaataacatc ttcaaactca	1080
cctcatgtgg tcaaaacagc cactcaaggg gaggtcaatg tgactggtgt gataccacta	1140
acaacaacac caacaaaatc ttattttgca aatctcaaag gaacaaggac cagagggaaa	1200
ctatgcccag actgtctcaa ctgcacagat ctggatgtgg ctttgggcag accaatgtgt	1260
gtggggacca caccttcggc gaaggcttca atactccacg aagtcacaac tgttacatcc	1320

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gggtgctttc ctataatgca cgacagaaca aaaatcaggc aactacccaa ttttctcaga 1380
ggatatgaaa atatcaggct atcaacccaa aacgtcatcg atgcggaaaa ggcaccagga 1440
ggaccctaca gacttggaac ctcaggatct tgccttaacg ctaccagtaa gagcggattt 1500
ttcgcaacaa tggttgggc tgtcccaaag gacaacaaca aaaatgcaac gaaccacta 1560
acagtagaag taccatacat ttgtacagaa ggggaagacc aaatcactgt ttgggggttc 1620
cattcagata acaaaaccca aatgaagaac ctctatggag actcaaatcc tcaaagttc 1680
acctcatctg ctaatggagt aaccacacac tatgtttctc agattggcag cttcccagat 1740
caaacagaag acggaggact accacaaagc ggcaggattg ttgttgatta catgatgcaa 1800
aaacctggga aaacaggaac aattgtctac caaagagggt ttttgttgcc tcaaaggtg 1860
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catgcaaaag ccataggaaa ttgcccaata tgggtgaaaa cacctttgaa gctcgccaat 2040
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gctggtttcc tagaaggagg atgggaagga atgattgcag gctggcacgg atacacatct 2160
cacggagcac atggagtggc agtggcggcg gaccttaaga gtacgcaaga agctataaac 2220
aagataacaa aaaatctcaa tcttttgagt gagctagaag taaagaatct tcaaagacta 2280
agtggtgcca tggatgaact ccacaacgaa atactcgagc tggatgagaa agtggatgat 2340
ctcagagctg acactataag ctgcgcaata gaacttgagc tcttgcttcc caacgaagga 2400
ataataaaca gtgaagatga gcatctattg gcacttgaga gaaaactaaa gaaaatgctg 2460
ggtcctctg ctgtagagat aggaaatgga tgcttcgaaa ccaaacacaa gtgcaaccag 2520
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ggtgtaatgt aattcattta cataagtgga gtcagaatca gaatgtttcc tccataacta 2940
actagacatg aagacctgcc gcgtacaatt gtcttatatt tgaacaacta aaattgaaca 3000
tcttttgcca caactttata agtggtaaat atagctcaaa tatatggcca agttcaatag 3060
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actaatttta tatcatcccc tttgataaat gatagtaca 3159

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<210> SEQ ID NO 74
<211> LENGTH: 565
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Consensus
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (52)..(52)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<222> LOCATION: (90)..(90)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (99)..(99)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (111)..(111)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (145)..(145)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (157)..(157)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<221> NAME/KEY: misc_feature
<222> LOCATION: (162)..(162)
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<221> NAME/KEY: misc_feature
<222> LOCATION: (182)..(182)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
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<222> LOCATION: (203)..(203)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<221> NAME/KEY: misc_feature
<222> LOCATION: (210)..(210)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
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<222> LOCATION: (225)..(225)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<222> LOCATION: (268)..(268)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
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<221> NAME/KEY: misc_feature
<222> LOCATION: (283)..(283)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (290)..(290)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (432)..(432)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (489)..(489)
<223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid

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<400> SEQUENCE: 74

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Met Lys Xaa Lys Leu Leu Val Leu Leu Cys Thr Phe Thr Ala Thr Tyr
1             5             10             15

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Ala Asp Thr Ile Cys Ile Gly Tyr His Ala Asn Asn Ser Thr Asp Thr
20             25             30

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Val Asp Thr Val Leu Glu Lys Asn Val Thr Val Thr His Ser Val Asn
35             40             45

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Leu Leu Glu Xaa Ser His Asn Gly Lys Leu Cys Leu Leu Lys Gly Ile
50             55             60

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Ala Pro Leu Gln Leu Gly Asn Cys Ser Val Ala Gly Trp Ile Leu Gly

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65	70	75	80
Asn Pro Glu Cys Glu Leu Leu Ile Ser Xaa Glu Ser Trp Ser Tyr Ile 85 90 95			
Val Glu Xaa Pro Asn Pro Glu Asn Gly Thr Cys Tyr Pro Gly Xaa Phe 100 105 110			
Ala Asp Tyr Glu Glu Leu Arg Glu Gln Leu Ser Ser Val Ser Ser Phe 115 120 125			
Glu Arg Phe Glu Ile Phe Pro Lys Glu Ser Ser Trp Pro Asn His Thr 130 135 140			
Xaa Thr Gly Val Ser Ala Ser Cys Ser His Asn Gly Xaa Ser Ser Phe 145 150 155 160			
Tyr Xaa Asn Leu Leu Trp Leu Thr Gly Lys Asn Gly Leu Tyr Pro Asn 165 170 175			
Leu Ser Lys Ser Tyr Xaa Asn Asn Lys Glu Lys Glu Val Leu Val Leu 180 185 190			
Trp Gly Val His His Pro Pro Asn Ile Gly Xaa Gln Xaa Ala Leu Tyr 195 200 205			
His Xaa Glu Asn Ala Tyr Val Ser Val Val Ser Ser His Tyr Ser Arg 210 215 220			
Xaa Phe Thr Pro Glu Ile Ala Lys Arg Pro Lys Val Arg Asp Gln Glu 225 230 235 240			
Gly Arg Ile Asn Tyr Tyr Trp Thr Leu Leu Glu Pro Gly Asp Thr Ile 245 250 255			
Ile Phe Glu Ala Asn Gly Asn Leu Ile Ala Pro Xaa Tyr Ala Phe Ala 260 265 270			
Leu Ser Arg Gly Phe Gly Ser Gly Ile Ile Xaa Ser Asn Ala Pro Met 275 280 285			
Asp Xaa Cys Asp Ala Lys Cys Gln Thr Pro Gln Gly Ala Ile Asn Ser 290 295 300			
Ser Leu Pro Phe Gln Asn Val His Pro Val Thr Ile Gly Glu Cys Pro 305 310 315 320			
Lys Tyr Val Arg Ser Ala Lys Leu Arg Met Val Thr Gly Leu Arg Asn 325 330 335			
Ile Pro Ser Ile Gln Ser Arg Gly Leu Phe Gly Ala Ile Ala Gly Phe 340 345 350			
Ile Glu Gly Gly Trp Thr Gly Met Val Asp Gly Trp Tyr Gly Tyr His 355 360 365			
His Gln Asn Glu Gln Gly Ser Gly Tyr Ala Ala Asp Gln Lys Ser Thr 370 375 380			
Gln Asn Ala Ile Asn Gly Ile Thr Asn Lys Val Asn Ser Val Ile Glu 385 390 395 400			
Lys Met Asn Thr Gln Phe Thr Ala Val Gly Lys Glu Phe Asn Lys Leu 405 410 415			
Glu Arg Arg Met Glu Asn Leu Asn Lys Lys Val Asp Asp Gly Phe Xaa 420 425 430			
Asp Ile Trp Thr Tyr Asn Ala Glu Leu Leu Val Leu Leu Glu Asn Glu 435 440 445			
Arg Thr Leu Asp Phe His Asp Ser Asn Val Lys Asn Leu Tyr Glu Lys 450 455 460			
Val Lys Ser Gln Leu Lys Asn Asn Ala Lys Glu Ile Gly Asn Gly Cys 465 470 475 480			
Phe Glu Phe Tyr His Lys Cys Asn Xaa Glu Cys Met Glu Ser Val Lys 485 490 495			

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Asn Gly Thr Tyr Asp Tyr Pro Lys Tyr Ser Glu Glu Ser Lys Leu Asn  
 500 505 510

Arg Glu Lys Ile Asp Gly Val Lys Leu Glu Ser Met Gly Val Tyr Gln  
 515 520 525

Ile Leu Ala Ile Tyr Ser Thr Val Ala Ser Ser Leu Val Leu Leu Val  
 530 535 540

Ser Leu Gly Ala Ile Ser Phe Trp Met Cys Ser Asn Gly Ser Leu Gln  
 545 550 555 560

Cys Arg Ile Cys Ile  
 565

&lt;210&gt; SEQ ID NO 75

&lt;211&gt; LENGTH: 565

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Influenza Virus

&lt;400&gt; SEQUENCE: 75

Met Lys Ala Lys Leu Leu Val Leu Leu Cys Thr Phe Thr Ala Thr Tyr  
 1 5 10 15

Ala Asp Thr Ile Cys Ile Gly Tyr His Ala Asn Asn Ser Thr Asp Thr  
 20 25 30

Val Asp Thr Val Leu Glu Lys Asn Val Thr Val Thr His Ser Val Asn  
 35 40 45

Leu Leu Glu Asp Ser His Asn Gly Lys Leu Cys Leu Leu Lys Gly Ile  
 50 55 60

Ala Pro Leu Gln Leu Gly Asn Cys Ser Val Ala Gly Trp Ile Leu Gly  
 65 70 75 80

Asn Pro Glu Cys Glu Leu Leu Ile Ser Lys Glu Ser Trp Ser Tyr Ile  
 85 90 95

Val Glu Thr Pro Asn Pro Glu Asn Gly Thr Cys Tyr Pro Gly Tyr Phe  
 100 105 110

Ala Asp Tyr Glu Glu Leu Arg Glu Gln Leu Ser Ser Val Ser Ser Phe  
 115 120 125

Glu Arg Phe Glu Ile Phe Pro Lys Glu Ser Ser Trp Pro Asn His Thr  
 130 135 140

Val Thr Gly Val Ser Ala Ser Cys Ser His Asn Gly Lys Ser Ser Phe  
 145 150 155 160

Tyr Arg Asn Leu Leu Trp Leu Thr Gly Lys Asn Gly Leu Tyr Pro Asn  
 165 170 175

Leu Ser Lys Ser Tyr Val Asn Asn Lys Glu Lys Glu Val Leu Val Leu  
 180 185 190

Trp Gly Val His His Pro Pro Asn Ile Gly Asn Gln Arg Ala Leu Tyr  
 195 200 205

His Thr Glu Asn Ala Tyr Val Ser Val Val Ser Ser His Tyr Ser Arg  
 210 215 220

Arg Phe Thr Pro Glu Ile Ala Lys Arg Pro Lys Val Arg Asp Gln Glu  
 225 230 235 240

Gly Arg Ile Asn Tyr Tyr Trp Thr Leu Leu Glu Pro Gly Asp Thr Ile  
 245 250 255

Ile Phe Glu Ala Asn Gly Asn Leu Ile Ala Pro Trp Tyr Ala Phe Ala  
 260 265 270

Leu Ser Arg Gly Phe Gly Ser Gly Ile Ile Thr Ser Asn Ala Pro Met  
 275 280 285

Asp Glu Cys Asp Ala Lys Cys Gln Thr Pro Gln Gly Ala Ile Asn Ser

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290					295					300					
Ser	Leu	Pro	Phe	Gln	Asn	Val	His	Pro	Val	Thr	Ile	Gly	Glu	Cys	Pro
305					310					315					320
Lys	Tyr	Val	Arg	Ser	Ala	Lys	Leu	Arg	Met	Val	Thr	Gly	Leu	Arg	Asn
				325					330					335	
Ile	Pro	Ser	Ile	Gln	Ser	Arg	Gly	Leu	Phe	Gly	Ala	Ile	Ala	Gly	Phe
			340					345					350		
Ile	Glu	Gly	Gly	Trp	Thr	Gly	Met	Val	Asp	Gly	Trp	Tyr	Gly	Tyr	His
		355					360					365			
His	Gln	Asn	Glu	Gln	Gly	Ser	Gly	Tyr	Ala	Ala	Asp	Gln	Lys	Ser	Thr
	370					375					380				
Gln	Asn	Ala	Ile	Asn	Gly	Ile	Thr	Asn	Lys	Val	Asn	Ser	Val	Ile	Glu
385					390					395					400
Lys	Met	Asn	Thr	Gln	Phe	Thr	Ala	Val	Gly	Lys	Glu	Phe	Asn	Lys	Leu
				405					410					415	
Glu	Arg	Arg	Met	Glu	Asn	Leu	Asn	Lys	Lys	Val	Asp	Asp	Gly	Phe	Leu
			420					425					430		
Asp	Ile	Trp	Thr	Tyr	Asn	Ala	Glu	Leu	Leu	Val	Leu	Leu	Glu	Asn	Glu
		435					440						445		
Arg	Thr	Leu	Asp	Phe	His	Asp	Ser	Asn	Val	Lys	Asn	Leu	Tyr	Glu	Lys
	450					455					460				
Val	Lys	Ser	Gln	Leu	Lys	Asn	Asn	Ala	Lys	Glu	Ile	Gly	Asn	Gly	Cys
465					470					475					480
Phe	Glu	Phe	Tyr	His	Lys	Cys	Asn	Asn	Glu	Cys	Met	Glu	Ser	Val	Lys
				485					490					495	
Asn	Gly	Thr	Tyr	Asp	Tyr	Pro	Lys	Tyr	Ser	Glu	Glu	Ser	Lys	Leu	Asn
			500					505					510		
Arg	Glu	Lys	Ile	Asp	Gly	Val	Lys	Leu	Glu	Ser	Met	Gly	Val	Tyr	Gln
		515					520					525			
Ile	Leu	Ala	Ile	Tyr	Ser	Thr	Val	Ala	Ser	Ser	Leu	Val	Leu	Leu	Val
	530					535					540				
Ser	Leu	Gly	Ala	Ile	Ser	Phe	Trp	Met	Cys	Ser	Asn	Gly	Ser	Leu	Gln
545					550					555					560
Cys	Arg	Ile	Cys	Ile											
				565											

&lt;210&gt; SEQ ID NO 76

&lt;211&gt; LENGTH: 252

&lt;212&gt; TYPE: PRT

&lt;213&gt; ORGANISM: Influenza Virus

&lt;400&gt; SEQUENCE: 76

Met	Ser	Leu	Leu	Thr	Glu	Val	Glu	Thr	Tyr	Val	Leu	Ser	Ile	Ile	Pro
1				5					10					15	
Ser	Gly	Pro	Leu	Lys	Ala	Glu	Ile	Ala	Gln	Arg	Leu	Glu	Asp	Val	Phe
			20					25					30		
Ala	Gly	Lys	Asn	Thr	Asp	Leu	Glu	Val	Leu	Met	Glu	Trp	Leu	Lys	Thr
		35					40					45			
Arg	Pro	Ile	Leu	Ser	Pro	Leu	Thr	Lys	Gly	Ile	Leu	Gly	Phe	Val	Phe
	50					55					60				
Thr	Leu	Thr	Val	Pro	Ser	Glu	Arg	Gly	Leu	Gln	Arg	Arg	Arg	Phe	Val
65					70					75					80
Gln	Asn	Ala	Leu	Asn	Gly	Asn	Gly	Asp	Pro	Asn	Asn	Met	Asp	Lys	Ala
				85					90					95	

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Val Lys Leu Tyr Arg Lys Leu Lys Arg Glu Ile Thr Phe His Gly Ala  
 100 105 110

Lys Glu Ile Ser Leu Ser Tyr Ser Ala Gly Ala Leu Ala Ser Cys Met  
 115 120 125

Gly Leu Ile Tyr Asn Arg Met Gly Ala Val Thr Thr Glu Val Ala Phe  
 130 135 140

Gly Leu Val Cys Ala Thr Cys Glu Gln Ile Ala Asp Ser Gln His Arg  
 145 150 155 160

Ser His Arg Gln Met Val Thr Thr Thr Asn Pro Leu Ile Arg His Glu  
 165 170 175

Asn Arg Met Val Leu Ala Ser Thr Thr Ala Lys Ala Met Glu Gln Met  
 180 185 190

Ala Gly Ser Ser Glu Gln Ala Ala Glu Ala Met Glu Val Ala Ser Gln  
 195 200 205

Ala Arg Gln Met Val Gln Ala Met Arg Thr Ile Gly Thr His Pro Ser  
 210 215 220

Ser Ser Ala Gly Leu Lys Asn Asp Leu Leu Glu Asn Leu Gln Ala Tyr  
 225 230 235 240

Gln Lys Arg Met Gly Val Gln Met Gln Arg Phe Lys  
 245 250

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What is claimed is:

1. A method of producing influenza virus like particles (VLPs) in a plant, the VLPs comprising protein, wherein the protein consists of influenza hemagglutinin (HA), comprising:
  - a) introducing a nucleic acid comprising a nucleotide sequence encoding the hemagglutinin (HA) operatively linked to a regulatory region active in the plant into the plant, or portion thereof,
  - b) incubating the plant under conditions that permit the expression of the nucleic acid, thereby producing the VLPs comprising protein, wherein the protein consists of influenza hemagglutinin (HA),
  - c) harvesting the plant, and
  - d) purifying the VLPs, wherein the VLPs range in size from 80-300 nm.
2. The method of claim 1, wherein the HA is selected from the group of H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, and H16.
3. The method of claim 2, wherein in the step of introducing (step a), the nucleic acid is transiently expressed in the plant.
4. The method of claim 2, wherein, in the step of introducing (step a), the nucleic acid is stably expressed in the plant.
5. A virus like particle (VLP) produced by the method of claim 1, wherein the VLP further comprises one or more than one lipid derived from a plant.
6. The VLP of claim 5, wherein the HA is H5 Indonesia.
7. A composition comprising an effective dose of the VLP of claim 5 for inducing an immune response, and a pharmaceutically acceptable carrier.

8. A VLP produced by the method of claim 1, wherein the HA comprises plant-specific N-glycans, or modified N-glycans.
9. The VLP of claim 5, for use in inducing immunity to an influenza virus infection in a subject.
10. The VLP of claim 9, wherein the VLP is suitable for oral, intradermal, intranasal, intramuscular, intraperitoneal, intravenous, or subcutaneous administration.
11. A composition comprising an effective dose of the VLP of claim 8 for inducing an immune response and a pharmaceutically acceptable carrier.
12. The composition of claim 11 for use in inducing immunity to an influenza virus infection in a subject.
13. The composition of claim 12, wherein the composition is suitable for oral, intradermal, intranasal, intramuscular, intraperitoneal, intravenous, or subcutaneous administration.
14. A food supplement comprising the VLP of claim 5.
15. A virus like particle (VLP) produced by the method of claim 2, wherein the VLP further comprises one or more than one lipid derived from a plant.
16. A composition comprising an effective dose of the VLP of claim 15 for inducing an immune response, and a pharmaceutically acceptable carrier.
17. A VLP produced by the method of claim 2, wherein the HA comprises plant-specific N-glycans, or modified N-glycans.
18. The VLP of claim 17, for use in inducing immunity to an influenza virus infection in a subject.
19. The VLP of claim 17, wherein the VLP is suitable for oral, intradermal, intranasal, intramuscular, intraperitoneal, intravenous, or subcutaneous administration.

\* \* \* \* \*